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December 8, 1993

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Attention: Section 8(e) Coordinator

Dear Sir/Madam:

Enclosed is a draft report of an oral gavage teratology study in the rat on "IPPD":

**N-isopropyl-N'-phenyl-para-phenylenediamine (CAS #101-72-4).**

This study was performed on behalf of a joint-industry group consisting of Monsanto, Uniroyal and Akzo. The test material is representative of products made by each company. A copy of the final report will be submitted to the Agency when it is received.

The study results indicate that treating pregnant rats with the material was associated with an increased rate of skeletal variations in the fetuses at the highest dose (125 mg/kg).

Although the findings are not considered to be indicative of substantial risk, we are providing the report in order to satisfy any reporting obligations that the Agency may consider necessary.

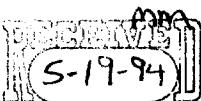
Sincerely,

Ronald D. Hogue

Ronald D. Hogue, Ph.D.  
Manager, Product Safety

Enclosure

cc: Dr. A. Taylor - Uniroyal  
Dr. F. Verhelst - Akzo



A Unit of Monsanto Company

232 pg's

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IPPD:

ORAL GAVAGE TERATOLOGY

STUDY IN THE RAT

PROJECT NUMBER: 543/2

Experimental Procedures: Date of Start of Dosing: 10 May 1993  
Date of Completion of Dosing: 30 May 1993  
Date of Final Necropsy: 4 June 1993

AUTHOR: R.J. Coles

STUDY SPONSOR:

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SAFEPHARM LABORATORIES LIMITED

QUALITY ASSURANCE UNIT REPORT

The conduct of this study has been subjected to periodic inspections by Safepharm Laboratories Quality Assurance Unit. The dates of inspection are given below:

16/03/93, 07/05/93, 10/05/93, 19/05/93, 21/05/93, 26/05/93, 07/06/93,  
24/06/93

This report has been audited by Safepharm Laboratories Quality Assurance Unit and is an accurate account of the procedures followed and accurately records the original raw laboratory data generated in this study.

Date of report audit: 04/11/93

J.R. Pateman M.I. Biol., C. Biol.  
QUALITY ASSURANCE MANAGER .....

DATE: .....



GLP COMPLIANCE STATEMENT

I, the undersigned, hereby declare that this report fully and accurately reflects the procedures used and data generated in the study, and that the work was performed in compliance with the following principles of Good Laboratory Practice.

Good Laboratory Practice, The United Kingdom Compliance Programme, Department of Health 1989.

Organisation for Economic Co-operation and Development, ISBN 92-64-12367-9, Paris 1982.

United States Environmental Protection Agency, Title 40, Code of Federal Regulations, Part 160 and Part 792; and United States Food and Drug Administration, Title 21 Code of Federal Regulations Part 58.

Japanese Ministry of Agriculture, Forestry and Fisheries, 59 NohSan Notification No. 3850, Agricultural Production Bureau, 10 August 1984.

Japanese Ministry of Health and Welfare, Notification No. Yakuhsatsu 313, Pharmaceutical Affairs Bureau, 31 March 1982 and subsequent amendment Notification No. Yakuhsatsu 870, Pharmaceutical Affairs Bureau, 5 October 1988.

..... DATE: .....

R.J. Coles B.Sc. (Hons)  
Study Director



AUTHENTICATION

I, the undersigned, hereby declare that the foetal evaluation data presented in this report were compiled by me or under my supervision and accurately reflect the data obtained.

..... DATE: .....

R.J. Coles B.Sc. (Hons)  
Necropsy and Foetal Evaluation Supervisor

I, the undersigned, hereby declare that the analytical data presented in this report were compiled by me or under my supervision and accurately reflect the data obtained.

..... DATE: .....

A.J. Bartlett L.R.S.C.  
Head of Analytical Chemistry

Approved for Issue:

..... DATE: .....

E. Wood C. Biol., M.I. Biol.  
Head of Reproductive Toxicology

The following scientific and supervisory personnel were involved in the study under the overall supervision of the Study Director.

E. Wood C. Biol., M.I. Biol.



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P A R T   I

IPPD:

ORAL GAVAGE TERATOLOGY STUDY

IN THE RAT

PROJECT NUMBER: 543/2



IPPD:

ORAL GAVAGE TERATOLOGY

STUDY IN THE RAT

SUMMARY

Groups of twenty-four mated female Sprague-Dawley CD strain rats were dosed orally, by gavage, with IPPD from day six to fifteen of gestation inclusive. The dose levels were 12.5, 62.5, 125 mg, IPPD/kg bodyweight, with a concurrent control group dosed with vehicle only.

Individual clinical observations, bodyweight and food consumption were recorded during the study. The females were killed on day twenty of gestation, examined macroscopically and the uterine contents examined. The number of corpora lutea, implantation number, position and type, foetal weights, foetal sex and external appearance were recorded. All live foetuses were preserved, processed and subsequently examined for skeletal or visceral anomalies.

RESULTS

Adults

At 125 and 62.5 mg/kg a reduction in food consumption was seen from day 6 to 9 of gestation.

At 125 mg/kg observations of pre-dosing salivation and soft dark faeces were recorded.

Litters

At 125 mg/kg a statistically significant increase in the number of foetuses with skeletal findings was noted.

CONCLUSION

Treatment of pregnant females with IPPD at a dose level of 125 mg/kg resulted in slight maternal toxicity and a statistically significant increase in the number of foetuses with skeletal findings. The no observed effect level for maternal toxicity was 12.5 mg/kg. The no observed effect level for offspring was 62.5 mg/kg.

that does not coincide with p.25 information, which indicates variations down to the lowest test level.

IPPD:

ORAL GAVAGE TERATOLOGY

STUDY IN THE RAT

1. INTRODUCTION

The objective of this study was to investigate the effects of IPPD when administered orally, by gavage, to pregnant rats during the period of embryo organogenesis.

The study was designed to comply with Principle Regulatory Guidelines.

The study was conducted in accordance with the internationally accepted general principles of Good Laboratory Practice and Safepharm Standard Operating Procedures.

The in-life phase of this study was conducted between 4 May 1993 and 4 June 1993 (see Appendix X).

2. TEST MATERIAL

2.1 Description, Identification and Storage Conditions

The test material was supplied as follows:

Sponsor's identification	:	Flexzone 3C
Chemical name	:	N-phenyl-N'-isopropyl-p-phenylene diamine
Batch number	:	02240
Date received	:	28 January 1993
Description	:	dark brown/grey flakes
Container	:	opaque plastic tub
Storage conditions	:	room temperature
Purity (%)*	:	97.2
Supplied by	:	Uniroyal Chemical Company Inc Elm Street Naugatuck Connecticut 06770

Data relating to the identity and stability of the test material are the responsibility of the sponsor.

\* Purity determined by Safepharm Laboratories Ltd. (see Appendix XII).

2. TEST MATERIAL

2.2 Method of Preparation

Prior to dose preparation, IPPD was ground into a powder using a pestle and mortar.

IPPD was dissolved in Polyethylene Glycol 400 (vehicle) weekly by weighing an amount of the test material into a suitable container and adding vehicle to make the appropriate final volume. Intermediate and low dose formulations were prepared by diluting the initial formulation. Homogeneity was assured by mixing the formulations with a Silverson mixer/homogeniser.

2.3 Dose Levels and Administration

The dose levels are presented in the following table and were selected on the basis of results of a range-finding study after consultation with the study sponsor (see Part II of this report).

GROUP NUMBER	GROUP DESCRIPTION	DOSE LEVEL (mg/kg)	DOSE CONCENTRATION (mg/ml)
1	Control	0	0
2	Low	12.5	2.5
3	Intermediate	62.5	12.5
4	High	125	25

The test material and vehicle were administered using a plastic catheter and plastic syringe at a constant dose volume of 5 ml/kg bodyweight.

Oral gavage administration was chosen as it represents a route of potential human exposure.

2.4 Analysis of Dose Preparations

Prior to the start of the study a procedure was developed to prepare the test material for dose administration. These preparations were analysed for achieved concentration and stability.

2. TEST MATERIAL (contd)

2.4 Analysis of Dose Preparations (contd)

During the dosing period of this study samples of the dose preparations were taken. The samples were analysed for achieved concentration.

The methods of analysis and the results of these analyses are presented in Appendix XI.

3. TEST SYSTEM

3.1 Specification

One hundred and thirteen virgin female Sprague-Dawley CD strain rats were obtained from Charles River (U.K.) Limited, Manston, Kent. Additionally, twenty-five sexually mature male Sprague-Dawley CD strain rats were obtained for mating purposes only.

On arrival the animals were examined and found to be in good health. The age range of the females on arrival was 9 to 12 weeks. The females were acclimatised to the laboratory conditions for at least 21 days before mating.

3.2 Justification

The rat was chosen for this study as it represents the species historically used for safety evaluation studies and is specified by the principle regulatory authorities.

3.3 Husbandry

The animals were housed in a single air-conditioned room, providing at least 15 air changes per hour. The room was maintained to operate within a temperature range of 19 and 25°C and a relative humidity of 40 and 75%, with these conditions monitored on a daily basis. The lighting within the room was controlled to allow 12 hours of continuous light within a 24-hour period.

3. TEST SYSTEM (contd)

3.3 Husbandry (contd)

Upon arrival, the females were housed in groups of five in polypropylene cages with stainless steel grid floors and lids, suspended over paper-lined polypropylene trays. During the mating period females were transferred to a similar type of cage with a sexually mature male on a maximum two female : 1 male basis.

Following evidence of successful mating, the animals were caged individually in polypropylene cages with solid floors and stainless steel grid tops. Autoclaved sawdust was used as bedding material.

Throughout the study the animals were given pelleted diet (SQC Rat and Mouse Breeder Diet No. 3 Expanded, Special Diet Services Limited, Witham, Essex, U.K.) ad libitum.

The animals were given water from plastic bottles attached to each cage, ad libitum.

The diet and water were considered not to have contained any contaminants at a level which may have affected the outcome of this study.

4. PROCEDURES

4.1 Mating

Females were housed with males on a 2 female : 1 male basis. The following morning each tray was checked for the presence of ejected copulation plugs. All females were checked for copulation plugs in situ, and then a vaginal smear was taken to check for the presence of sperm. Females showing evidence of sperm within the vaginal smear were separated from the male and designated day 0 of gestation. These females were replaced with previously unmated females. The total mating period for this study was 12 days.

4. PROCEDURES (contd)

4.2 Allocation

Immediately after mating the females were assigned to treatment groups using a randomisation procedure based on stratified bodyweight to ensure comparable group mean bodyweights for each treatment group. The weight range of females at allocation was 223 to 311 grams. The females were assigned to positions on the cage battery using a randomised block design.

4.3 Animal Identification

At allocation females were given a unique earmark for the study according to the assigned number for each dose group. Each cage was identified with a colour coded card containing information including project number, dose group and animal number, as follows:

DOSE GROUP	COLOUR* CODE	NUMBER OF ANIMALS ASSIGNED	ANIMAL IDENTIFICATION NUMBER
1	Buff	24	1 - 24
2	Green	24	25 - 48
3	Blue	24	49 - 72
4	Red	24	73 - 96

\* for cage cards and raw data sheets

4.4 Dosing

Mated female rats were dosed according to dose group, once daily from day six to fifteen of gestation, inclusive. The dose administered was adjusted for bodyweight on each day.

The study was not designed to show proof of test material absorption.

## 5. OBSERVATIONS

### 5.1 Morbidity/Mortality

All females were checked twice daily during the normal working week and once daily at weekends.

### 5.2 Clinical Observations

All females were observed once daily, in the morning throughout gestation and, additionally, one hour after dosing, throughout the dosing period, for clinical signs of toxicity.

### 5.3 Bodyweight

All females were weighed on days 0, 3, 6 to 15 inclusive, 18 and 20 of gestation.

### 5.4 Food Consumption

Food consumption for individual animals was recorded for discrete periods throughout the study on days 0-3, 3-6, 6-9, 9-12, 12-15, 15-18 and 18-20 of gestation.

### 5.5 Terminal Studies

All surviving females were killed on day 20 of gestation by carbon dioxide asphyxiation. Each animal was examined externally and internally for macroscopic abnormalities. The uterus of any apparently non-pregnant female was dissected free and subsequently stained with 10% ammonium polysulphide and examined for implantations (Salewski 1964). The ovaries and uteri of pregnant females were removed, examined and the following data recorded:

- i) Number of corpora lutea
- ii) Number, position and type of intrauterine implantation

Implantation types were divided into:

Early Death - No visible distinction between placental/decidual tissue and embryonic tissue.

5. OBSERVATIONS (contd)

5.5 Terminal Studies (contd)

Late Death - Separate embryonic/foetal and placental tissue visible.

Dead Foetus - A foetus that had died shortly before necropsy. These were included as late deaths for reporting purposes.

All implantations and viable foetuses were numbered according to their intrauterine position as follows:

<u>Left Horn</u>	<u>Cervix</u>	<u>Right Horn</u>
L1 L2 L3 L4 L5 L6 L7 L8		R1 R2 R3 R4 R5 R6 R7 R8
V1 V2 V3 V4 V5 V6 V7 V8		V9 V10 V11 V12 V13 V14 V15 V16

V = viable foetus

- iii) Foetal sex
- iv) External foetal appearance
- v) Foetal weight
- vi) Placental weight

The foetuses were killed by intraperitoneal injection of sodium pentobarbitone. Alternate foetuses were identified using an indelible marker and placed in Bouin's fixative. After a minimum of 7 days, foetuses were transferred to 80% industrial methylated spirits (IMS) in distilled water and examined for visceral anomalies under a low power binocular microscope (Wilson 1965). The remaining foetuses were identified using colour coded wires and placed in 70% IMS in distilled water. The foetuses were eviscerated, processed and the skeletons stained with alizarin red (Dawson 1926). The foetuses were examined for skeletal development and anomalies.

6. EVALUATION OF DATA

Data were processed to give litter mean values, group mean values and standard deviations.

6. EVALUATION OF DATA (contd)

- i) Absolute bodyweight change of females during gestation was calculated and presented relative to day 6 of gestation (day 1 of treatment).
- ii) Percentage pre-implantation loss was calculated as:

$$\frac{\text{number of corpora lutea} - \text{number of implantations}}{\text{number of corpora lutea}} \times 100$$

percentage post-implantation loss was calculated as:

$$\frac{\text{number of implantations} - \text{number of live foetuses}}{\text{number of implantations}} \times 100$$

- iv) Statistical evaluation was performed for the following parameters:

Food consumption: one way analysis of variance followed by pairwise analysis of group values by Student's 't' test.

Skeletal findings: Chi-square test or Fisher's Exact test for small sample sizes.

7. RESULTS

7.1 Mortality Data

There were no deaths.

7.2 Clinical Observations (Table 1, Appendix I)

At 125 mg/kg clinical observations were limited to pre-dosing salivation noted in 10/23 animals and soft dark faeces noted for 6/23 animals.

At 62.5 mg/kg transient noisy respiration was noted in one animal.

7.3 Bodyweight (Tables 2 and 3, Appendices II and III)

a) There were no treatment related effects on bodyweight noted during pregnancy.

7.4 Food Consumption (Table 4, Appendix IV)

At 125 mg/kg there was a statistically significant ( $p < 0.001$ ) reduction in food consumption from day 6 to day 9 of gestation which coincides with the initiation of dosing. At 62.5 mg/kg there was also a statistically significant reduction in food consumption over this period ( $p < 0.01$ ). After day 9 of gestation food consumption in these two groups was comparable with control animals.

At 12.5 mg/kg there were no significant effects on food consumption throughout the study.

7.5 Terminal Studies

a) Adult Necropsy Data (Appendix I)

There were no treatment-related macroscopic findings for adult females at necropsy.

b) Uterine/Implantation Data (Table 6, Appendices V and VI)

There were no treatment-related effects on uterine/implantation data.

7. RESULTS (contd)

7.5 Terminal Studies (contd)

c) Foetal Data (Tables 7 - 10, Appendices VI - IX)

Throughout all groups there were three foetuses with significant structural anomalies. At 12.5 mg/kg one foetus, (dam 35, foetus 1) had an encephalocele, <sup>while</sup> ~~had~~ a <sup>second</sup> ~~further~~ foetus (dam 44, foetus 7) ~~had~~ having an interventricular septal defect. At 0 mg/kg one foetus (dam 14, foetus 5) had an interventricular septal defect, an atretic left atrium and mitral valve, right sided aorta, aortic arch and ductus arteriosus, no brachiocephalic trunk, no pulmonary trunk with a modified ductus arteriosus exiting from the right ventricle.

There were no intergroup differences in the incidence of foetal external findings.

At 125 mg/kg there were statistically significant effects on the incidence of skeletal findings. At this dose level there was an increased incidence of irregularly and incompletely ossified cranial and facial bones ( $p < 0.001$  -  $p < 0.05$ ). There was also an increased incidence of no ossification of hyoid ( $p < 0.001$ ), unilateral/ bilateral wavy ribs ( $p < 0.05$ ) and semi-bipartite vertebral centra ( $p < 0.01$ ).

At 62.5 mg/kg there was a statistically significant increase in incomplete ossification of more than one cranial bone ( $p < 0.05$ ).

At 12.5 mg/kg there was a statistically significant increase in incomplete ossification of more than one facial bone ( $p < 0.05$ ).

The overall incidence of visceral findings for foetuses was considered comparable for all groups. Intergroup variations for specific visceral findings were not considered to be significant.

### DISCUSSION

At 125 mg/kg there was a statistically significant reduction in food consumption from day 6 to day 9 of gestation which coincides with the initiation of dosing. After this period food consumption values were comparable with control values. Animals from <sup>the high-dose</sup> this group also showed clinical observations of pre-dosing salivation and soft dark faeces. These observations, combined with the reduction in food consumption, are indicative of slight maternal toxicity. No treatment-related effects on uterine/implantation data were noted at this dose level. Foetal external and visceral findings showed no treatment-related effects. However, the incidence of skeletal findings showed several statistically significant effects. The most marked of these was an increased incidence of irregularly and incompletely ossified cranial and facial bones. There was also a statistically significant increase of no ossification of hyoid, semi-bipartite vertebral centra and unilateral/bilateral wavy ribs. ~~These effects are considered indicative of general maternal/foetal toxicity.~~ In the absence of any other effects suggest that there is minimal effect on foetal development.

<sup>, these data</sup>  
<sup>without concurrent maternal toxicity</sup>

At 62.5 mg/kg there was a statistically significant reduction in food consumption from day 6 to day 9 of gestation which coincides with the initiation of dosing. After this period food consumption values were comparable with control values. The reduction in food consumption is thought to be indicative of slight maternal toxicity. Uterine/implantation data, foetal external and visceral findings all showed no treatment-related effects. Although there was a statistically significant increase in the number of foetuses having incomplete ossification of more than one cranial bone, in the absence of other skeletal findings this was considered not to be treatment-related. At 12.5 mg/kg there were no treatment related effects on adults, uterine/implantation data, foetal external or foetal visceral findings. There was a statistically significant increase in the number of foetuses with incomplete ossification of more than one facial bone, but in the absence of an effect on intermediate dose animals for this finding and the lack of any other findings, this was considered not to be treatment-related.

CONCLUSION

Treatment of pregnant females with IPPD at a dose level of 125 mg/kg resulted in slight maternal toxicity and a statistically significant increase in the number of foetuses with skeletal findings. The no observed effect level for maternal toxicity was 12.5 mg/kg. The no observed effect level for offspring was 62.5 mg/kg.

ARCHIVE

Unless instructed otherwise by the sponsor, all original data, specimens and a copy of the final report will be retained in the archives of Safepharm Laboratories for a period of ten years. After this period, the sponsor's instructions will be sought.

Specimens will be taken to include test material, any tissues, or foetal specimens derived from the test system for examination or analysis.

Primary data will be taken to include laboratory data sheets, computer print-outs, records, memoranda, file notes and photographs that are a result of the original observations and activities of the study and which are necessary for the reconstruction and evaluation of the report of the study.

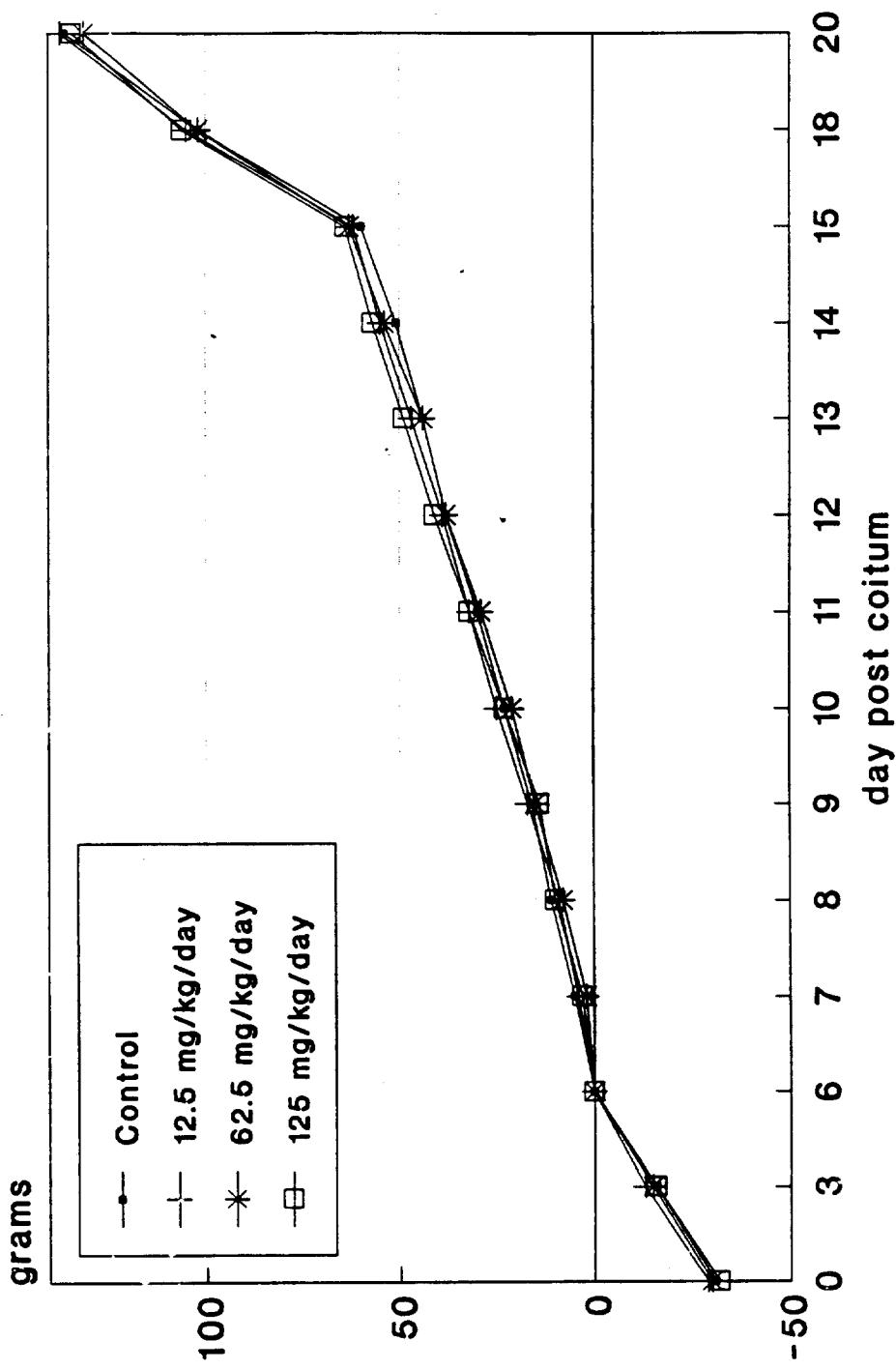
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2. Salewski E., (1964). Färbemethode zum makroskopischen Nachweis von Implantationsstellen am uterus der Ratte. *Naunyn - Schmiedebergs Arch. exp. Pathol. Pharmacol.* 247 367.
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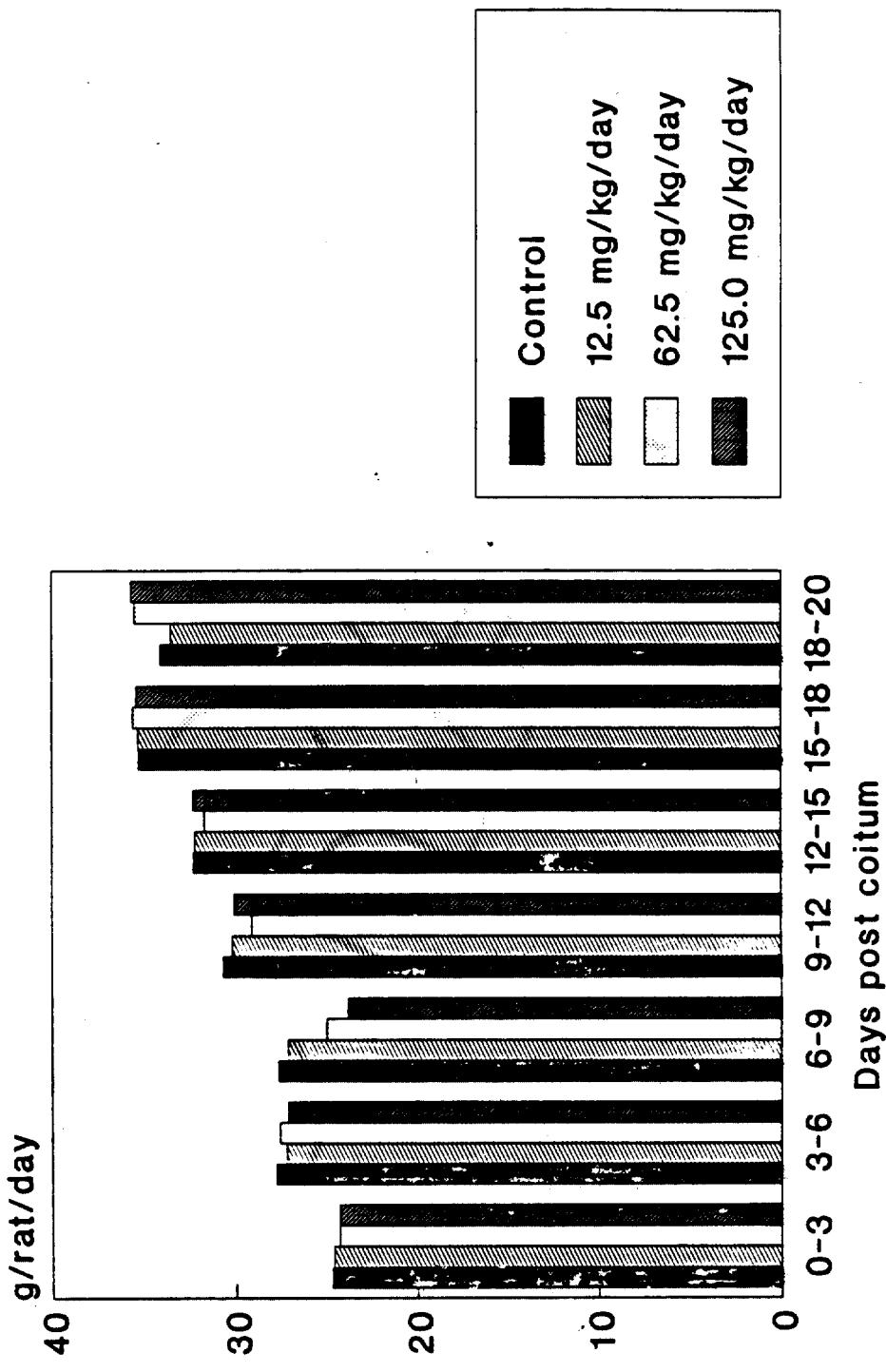
F I G U R E S

FIGURE 1  
GROUP MEAN BODYWEIGHT CHANGE (g)  
OF PREGNANT FEMALES POST COITUM\*



\* = Relative to day 6 post coitum

FIGURE 11 GROUP MEAN FOOD CONSUMPTION (g/rat/day)  
OF PREGNANT FEMALES POST COITUM





T A B L E S

**TABLE 1**  
**IPPD : ORAL GAVAGE TERATOLOGY STUDY IN THE RAT**  
**SUMMARY INCIDENCE OF DAILY CLINICAL OBSERVATIONS**

Group	Dose Level mg/kg Bodyweight	Clinical Observations	Number of Animals Affected	Group Mean Day of Observation		
				First Recorded	Last Recorded	
1	0	No abnormalities detected	-	-	-	
2	12.5	No abnormalities detected	-	-	-	
3	62.5	Noisy respiration	1	7	8	
4	125	Salivation immediately before dosing Faeces - soft and dark	10	6	12.1 13.3	13.2 15.7

TABLE 2 GROUP MEAN BODYWEIGHT (g) OF PREGNANT FEMALES POST COITUM

Group	Dose Level mg/kg	Day Post Coitum														
		0	3	6	7	8	9	10	11	12	13	14	15	18	20	
1	0	Mean	269	284	300	305	311	316	323	330	337	344	351	360	402	436
		S.D.	16.8	20.2	22.2	23.0	23.5	21.9	20.9	20.9	22.5	22.0	22.7	22.9	27.6	29.9
		N	24	24	24	24	24	24	24	24	24	24	24	24	24	
2	12.5	Mean	270	287	300	303	308	317	324	332	338	346	354	362	405	436
		S.D.	14.6	15.6	14.6	14.8	16.1	16.6	16.5	18.2	18.9	19.0	19.2	19.7	23.3	27.8
		N	24	24	24	24	24	24	24	24	24	24	24	24	24	
3	62.5	Mean	269	285	299	302	308	314	320	329	337	344	353	362	401	431
		S.D.	17.5	18.7	19.8	19.4	20.8	19.9	20.7	22.0	21.7	22.7	22.6	22.9	28.3	32.3
		N	24	24	24	24	24	24	24	24	24	24	24	24	24	
4	125	Mean	265	282	297	300	307	311	321	329	338	346	354	361	403	431
		S.D.	15.2	15.6	16.5	16.1	18.5	19.9	20.2	18.8	20.6	20.4	21.1	22.2	25.3	28.1
		N	23	23	23	23	23	23	23	23	23	23	23	23	23	

S.D. = standard deviation

N = number of pregnant animals

TABLE 3  
GROUP MEAN BODYWEIGHT CHANGE (g) OF PREGNANT FEMALES POST COITUM\*

Group	Dose Level mg	Day Post Coitum													
		0	3	6	7	8	9	10	11	12	13	14	15	18	20
1 0	Mean	-31	-16	*	5	11	16	23	30	38	44	51	60	102	136
	S.D.	8.2	4.8		4.0	3.9	7.4	7.0	6.5	8.2	7.2	8.0	9.1	15.1	21.3
	N	24	24		24	24	24	24	24	24	24	24	24	24	
2 12.5	Mean	-29	-13	*	4	9	17	25	32	39	47	55	62	105	137
	S.D.	6.3	6.3		4.5	5.3	6.2	6.9	7.6	7.9	9.1	9.8	11.2	14.7	19.7
	N	24	24		24	24	24	24	24	24	24	24	24	24	
3 62.5	Mean	-30	-15	*	2	8	15	21	29	38	44	54	63	102	131
	S.D.	9.1	7.2		8.0	7.9	7.4	6.5	8.6	7.9	8.8	10.0	10.7	15.8	21.0
	N	24	24		24	24	24	24	24	24	24	24	24	24	
4 125	Mean	-32	-16	*	3	10	14	23	32	41	49	57	64	106	134
	S.D.	6.8	6.3		5.3	9.2	11.3	11.7	9.7	12.3	12.4	13.8	14.6	18.7	24.5
	N	23	23		23	23	23	23	23	23	23	23	23	23	

S.D. = standard deviation

N = number of animals

\* = relative to day 6 post coitum

**TABLE 4**  
**GROUP MEAN FOOD CONSUMPTION (g/RAT/DAY) OF PREGNANT FEMALES POST COITUM**

Group	Dose Level mg/kg	Days Post Coitum							
		0-3	3-6	6-9	9-12	12-15	15-18		
1	0	Mean	24.7	27.8	27.7	30.7	32.3	35.3	34.1
		S.D.	2.38	2.81	2.61	2.96	2.54	2.50	2.42
		N	24	24	24	24	24	24	24
2	12.5	Mean	24.6	27.2	27.1	30.2	32.2	35.3	33.5
		S.D.	2.39	2.77	3.04	2.99	3.57	3.12	3.77
		N	24	24	24	24	24	24	24
3	62.5	Mean	24.3	27.6	25.0**	29.1	31.7	35.6	35.5
		S.D.	3.33	2.75	3.27	3.07	2.63	3.11	3.02
		N	24	24	24	24	24	24	24
4	125	Mean	24.3	27.1	23.8***	30.1	32.3	35.4	35.7
		S.D.	2.44	2.34	3.87	3.21	2.96	2.49	3.18
		N	23	23	23	23	23	23	23

S.D. = standard deviation  
\*\* = significantly different from control ( $p < 0.01$ )  
\*\*\* = significantly different from control ( $p < 0.001$ )

N = number of pregnant animals

IPPO : ORAL GAVAGE TERATOLOGY STUDY IN THE RAT

TABLE 5  
SUMMARY OF ADULT PERFORMANCE

	Dose Level mg/kg	0	12.5	62.5	125
Number of females in group	24	24	24	24	24
Number pregnant	24	24	24	23	
Number died/killed before day 20	0	0	0	0	0
Number not pregnant	0	0	0	0	1
Number with total litter loss	0	0	0	0	0

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TABLE 6 GROUP MEAN LITTER DATA

Group	Dose Level (mg/kg)	Number of Animals	Number Pregnant	Number of Corpora Lutea	Number of Live Foetuses	Number of Male Foetuses	Embryonic/Foetal Deaths			Implantation Loss %			Mean Weight (g)	Total Litter Weight (g)	Mean Foetal Weight (g)
							Early	Late	Total	Pre	Post				
1	0	24	24	18.4	15.0	49.4	0.54	0.00	0.54	14.9	3.4	55.7	3.72		
2	12.5	24	24	18.5	15.2	48.1	0.83	0.00	0.83	12.6	5.2	59.2	3.91		
3	62.5	24	24	18.6	13.8	46.8	0.96	0.00	0.96	20.3	7.5	52.9	3.80		
4	125	24	23	20.1	16.1	45.9	0.48	0.09	0.57	15.7	3.8	62.4	3.88		

TABLE 7  
GROUP INCIDENCE OF FOETAL EXTERNAL FINDINGS

External Findings	Number of Foetuses Examined						Dose Level mg/kg		
	0			12.5			62.5		
Total Number Affected	361	364	332	370	125	361	364	332	370
NF	NL	%*	NF	NL	%*	NF	NL	%*	NF
a - small foetus	2	2	0.6	2	2	0.6	5	4	2.8
b - pale foetus	1	1	0.3	0	0	-	0	0	0
c - reddened foetus	0	0	-	0	0	-	2	1	1.7
d - haemorrhage on hind foot	0	0	-	1	1	0.3	0	0	-
e - blood filled amniotic sac	0	0	-	1	1	0.3	0	0	-
f - encephalocele	0	0	-	1	1	0.3	0	0	-
g - haemorrhagic ring at base of tail	0	0	-	0	0	-	1	1	0.3
h - placenta enlarged and haemorrhagic	0	0	-	0	0	-	2	1	1.7
i - subcutaneous haemorrhage on head	0	0	-	0	0	-	0	0	-
j - blood in abdomen	0	0	-	0	0	-	1	1	0.3

NOTE: A foetus may appear in more than one category

\* = group mean per litter

NF = number of foetuses in category

NL = number of litters in category

TABLE 8  
GROUP INCIDENCE OF FOETAL VISCERAL FINDINGS

Visceral Findings	Dose Level mg/kg									
	0	12.5	62.5	125	Number of Foetuses Examined					
Total Number Affected	187	189	172	188	NF	NL	%*	NF	NL	%*
a - unilateral microphthalmia	1	1	0.5	0	0	1	1	0.7	0	0
aa - unilateral retinal infolding	0	0	-	1	0.5	1	1	0.5	0	0
b - ovoid lens(es) of eye(s)	3	3	1.4	5	4	2.7	11	7	7.9	5
c - enlarged brain ventricle(s)/ collecting duct	1	1	0.6	1	1	0.6	4	4	2.3	2
d - blood in nasal passages	0	0	-	0	0	-	0	-	1	1
e - haemorrhage within meningeal tissues	1	1	0.5	0	0	-	0	-	1	1
f - haemorrhage in back of brain/ pituitary area	0	0	-	0	0	-	0	-	1	1
g - subcutaneous haemorrhage on head	0	0	-	1	1	0.7	0	0	0	0

Code Finding

Head:

- a - unilateral microphthalmia
- aa - unilateral retinal infolding
- b - ovoid lens(es) of eye(s)
- c - enlarged brain ventricle(s)/ collecting duct
- d - blood in nasal passages
- e - haemorrhage within meningeal tissues
- f - haemorrhage in back of brain/ pituitary area
- g - subcutaneous haemorrhage on head

NOTE: A foetus may appear in more than one category

\* = group mean per litter

NF = number of foetuses in category

NL = number of litters in category

TABLE 8 (contd)                    GROUP INCIDENCE OF FOETAL VISCERAL FINDINGS

Visceral Findings	Number of Foetuses Examined						Dose Level mg/kg		
	187			189			172		
NF	NL	%*	NF	NL	%*	NF	NL	%*	
h - undescended lobe(s) of thymus	13	8	7.4	19	12	10.8	14	9	7.5
i - blood in oesophagus and/or trachea	0	0	-	1	0.5	0	0	-	1
j - short brachiocephalic trunk	0	0	-	0	0	-	1	1	0.5
k - no brachiocephalic trunk	1	1	0.5	0	0	-	0	0	-
l - pericardial oedema	0	0	-	1	1	0.4	0	0	0
m - interventricular septal defect	1	1	0.5	1	1	0.4	0	0	0
n - right sided aorta, aortic arch and ductus arteriosus	1	1	0.5	0	0	-	0	0	-
o - left atrium and mitral valve atretic	1	1	0.5	0	0	-	0	0	-
p - no pulmonary trunk, modified ductus arteriosus (exits from right ventricle)	1	1	0.5	0	0	-	0	0	-

Code Finding

Neck/Thorax:

- h - undescended lobe(s) of thymus
- i - blood in oesophagus and/or trachea
- j - short brachiocephalic trunk
- k - no brachiocephalic trunk
- l - pericardial oedema
- m - interventricular septal defect
- n - right sided aorta, aortic arch  
and ductus arteriosus
- o - left atrium and mitral valve atretic
- p - no pulmonary trunk, modified  
ductus arteriosus (exits from  
right ventricle)

NOTE: A foetus may appear in more than one category

\* = group mean per litter

NF = number of foetuses in category

NL = number of litters in category

TABLE 8 (contd) GROUP INCIDENCE OF FOETAL VISCERAL FINDINGS

Visceral Findings	Dose Level mg/kg					
	0	12.5	62.5	125		
Number of Foetuses Examined						
187	189	172	188			
NF	NL	%*	NF	NL	%*	NF
						NL
						%*

Code Finding	Abdomen	q - unilateral/bilateral small/no development of renal papilla(e)	r - unilateral/bilateral increased renal pelvic cavitation	s - unilateral/bilateral kinked and/or dilated ureter(s)	t - unilateral/bilateral dark adrenal medulla(e)	u - unilateral dark adrenal	v - unilateral small adrenal	w - immature liver	x - extra lobulation of liver median lobe	y - blood/haemorrhage in abdomen
		30	14	16.7	29	16	16.7	35	17	21.3
										38
										11
										18.7

NOTE: A foetus may appear in more than one category

\* = group mean per litter  
NF = number of foetuses in category  
NL = number of litters in category

TABLE 9  
GROUP SUMMARY OF FOETAL SKELETAL DEVELOPMENT

Skeletal Development	Dose Level mg/kg												
	Number of Foetuses Examined												
	0		12.5		62.5		125		182				
	NF	NL	%*	NF	NL	%*	NF	NL	%*	NF	NL	%*	
Number of ribs	13/13	153	24	89.1	152	24	87.2	143	24	90.1	154	23	82.7
	13/14	16	9	8.3	13	10	7.3	8	7	4.3	16	12	9.6
	14/14	5	3	2.5	10	7	5.4	7	6	5.6	12	6	7.7
Number of fully Ossified Sternebrae	<4	5	5	2.8	11	4	6.8	11	9	8.5	4	4	2.9
	4	69	19	38.0	54	18	32.4	52	21	36.2	75	21	40.7
	>4	99	24	59.2	107	23	60.8	94	20	55.3	103	22	56.4
Number of Post Lumbar Vertebrae	<7	8	6	4.5	8	5	4.1	12	7	9.6	7	5	3.6
	≥7	166	24	95.5	167	24	95.9	146	24	90.4	174	23	96.4
Number of Post Lumbar Vertebrae Arches	<5	26	12	16.0	27	12	16.7	33	13	19.6	23	12	12.3
	≥5	148	24	84.0	148	24	83.3	125	23	80.4	158	23	87.7

\* = group mean per litter

NF = number of foetuses in category

NL = number of litters in category

TABLE 9 (contd) GROUP SUMMARY OF FOETAL SKELETAL DEVELOPMENT  
IPPD : ORAL GAVAGE TERATOLOGY STUDY IN THE RAT

Skeletal Development	Dose Level mg/kg											
	0				12.5				62.5			
	Number of Foetuses Examined								125			
	174	175	179	182								
NF	NL	%*	NF	NL	%*	NF	NL	%*	NF	NL	%*	
Number of Metacarpals / Metatarsals	0/0	0	0	0	0	-	1	1	2.1	0	0	-
5/6	0	0	-	0	0	-	1	1	0.6	0	0	-
6/6	2	1.1	-	3	1.4	2	2	2.9	4	3	1.9	
6/7	0	0	-	1	0.6	0	0	-	2	2	1.1	
7/7	0	0	-	2	1	1.2	0	0	-	0	0	
4/8	0	0	-	1	1	0.5	0	0	-	0	0	
6/8	132	23	77.0	110	21	65.1	108	21	67.6	114	23	62.0
7/8	2	1	0.9	3	3	1.5	3	3	1.7	4	4	2.3
8/8	38	11	21.1	48	14	27.0	41	14	24.6	57	18	32.7
8/10	0	0	-	5	1	2.6	1	1	0.6	0	0	-
Fenestelle Size:												
Small	7	5	4.3	21	7	12.8	18	7	13.7	8	3	4.0
Medium	166	24	95.2	150	23	85.8	132	21	77.9	174	23	96.0
Large	1	1	0.5	3	2	1.4	9	4	8.4	0	0	-

\* = group mean per litter  
 NF = number of foetuses in category  
 NL = number of litters in category

TABLE 10  
GROUP INCIDENCE OF FOETAL SKELETAL FINDINGS

Skeletal Findings	Number of Foetuses Examined						Dose Level mg/kg					
	0			12.5			62.5					
	174	175	159		182							
NF	NL	%#	NF	NL	%#	NF	NL	%#	NL			
Total Number Affected	72	22	40.3	98	23	53.3	86	22	51.3	124	23	69.5

Head/Neck

- a - incomplete ossification of one cranial bone 20 12 11.2 25 14 13.3 12 9 7.1 29 16 16.0
- b - incomplete ossification of more than one cranial bone 12 10 6.9 13 9 7.5 25\* 11 15.2 35\*\* 16 17.8
- c - incomplete ossification of one facial bone 2 2 1.0 2 2 0.9 5 4 3.1 2 2 1.0
- d - incomplete ossification of more than one facial bone 2 2 1.1 10\* 5 5.3 6 6 5.1 19\*\*\* 10 10.0
- e - irregular ossification of one cranial bone 1 1 0.5 2 2 1.0 3 3 1.7 8\* 7 4.8
- f - irregular ossification of more than one cranial bone 1 1 0.6 1 1 0.5 0 0 - 1 1 0.5

NOTE: A foetus may appear in more than one category

\* = significantly different from control ( $p < 0.05$ )

\*\* = significantly different from control ( $p < 0.01$ )

\*\*\* = significantly different from control ( $p < 0.001$ )

# = group mean per litter

NF = number of foetuses in category

NL = number of litters in category

TABLE 10 (contd)  
GROUP INCIDENCE OF FOETAL SKELETAL FINDINGS

Skeletal Findings	Number of Foetuses Examined						Dose Level mg/kg		
	NF	NL	%#	NF	NL	%#	NF	NL	%#
Total Number Affected	72	22	40.3	98	23	53.3	86	22	51.3
							12.5	62.5	125
	174			175			159		182

Head/Neck (contd)

- g - irregular ossification of one facial bone
- h - irregular ossification of more than one facial bone
- i - no ossification of one cranial bone
- j - incomplete ossification of hyoid
- k - irregular ossification of hyoid
- l - no ossification of hyoid
- m - incomplete ossification of basisphenoid

NOTE: A foetus may appear in more than one category  
 \*\* = Significantly different from control ( $p < 0.01$ )  
 \*\*\* = Significantly different from control ( $p < 0.001$ )

# = group mean per litter  
 NF = number of foetuses in category  
 NL = number of litters in category

TABLE 10 (contd) GROUP INCIDENCE OF FOETAL SKELETAL FINDINGS

Skeletal Findings	Number of Foetuses Examined						Dose Level mg/kg		
	NF	NL	%#	NF	NL	%#	NF	NL	%#
Total Number Affected	72	22	40.3	98	23	53.3	86	22	51.3
							124	23	69.5
							125		

Head/Neck (contd)

n - enlarged frontal/nasal suture

o - miss-hapen frontals and parietals

Pectoral Girdle

p - incomplete ossification of scapula

q - unilateral/bilateral rudimentary  
13th rib(s)

r - unilateral/bilateral rudimentary  
14th rib(s)

s - unilateral/bilateral short rib(s)  
(excludes 14th ribs)

t - Bilateral short 14th ribs

NOTE: A foetus may appear in more than one category

# = group mean per litter

NF = number of foetuses in category

NL = number of litters in category

TABLE 10 (contd) GROUP INCIDENCE OF FOETAL SKELETAL FINDINGS

Skeletal Findings	Number of Foetuses Examined						Dose Level mg/kg	12.5	62.5	125	
	NF	NL	%#	NF	NL	%#					
Total Number Affected	72	22	40.3	98	23	53.3	86	22	51.3	124	23
											69.5
<u>Pectoral Girdle</u> (contd)											
u - unilateral/bilateral wavy ribs	1	1	0.6	0	0	-	2	2	1.1	7*	5
v - Bilateral thickened ribs	0	0	-	1	1	0.5	0	0	-	0	0
w - Bilateral incompletely ossified ribs	0	0	-	1	1	0.5	0	0	-	0	0
<u>Sternebrae</u>											
x - one sternebra incompletely ossified	1	1	0.5	1	1	0.6	5	3	2.8	1	1
y - more than one sternebra incompletely ossified	1	1	0.6	0	0	-	1	1	0.8	0	0
z - one sternebra not ossified	5	5	2.8	7	4	4.4	2	2	1.0	5	5
aa - more than one sternebra not ossified	0	0	-	1	1	0.5	2	2	2.9	0	0

NOTE: A foetus may appear in more than one category  
 \* = significantly different from control ( $p < 0.05$ )

# = group mean per litter

NF = number of foetuses in category

NL = number of litters in category

TABLE 10 (contd) GROUP INCIDENCE OF FOETAL SKELETAL FINDINGS

Skeletal Findings	Dose Level mg/kg											
	Number of Foetuses Examined											
	0	12.5	62.5	125								
NF	NL	%#	NF	NL	%#	NF						
174	175	159			182	%#						
Total Number Affected	72	22	40.3	98	23	53.3	86	22	51.3	124	23	69.5

Sternebrae (contd)	bb - one sternebra small	cc - more than one sternebra small	dd - one sternebra semi-bipartite	ee - more than one sternebra bipartite	ff - one sternebra misaligned	gg - more than one sternebra misaligned	hh - one sternebra assymmetric					
bb - one sternebra small	2	2	1.0	12	6	6.4	7	4	4.1	7	6	3.9
cc - more than one sternebra small	0	0	-	1	1	0.5	0	0	-	2	2	1.2
dd - one sternebra semi-bipartite	0	0	-	1	1	1.0	2	1	1.2	0	0	-
ee - more than one sternebra bipartite	1	1	0.5	0	0	-	0	0	-	0	0	-
ff - one sternebra misaligned	0	0	-	4	3	2.1	2	1	1.2	3	3	1.6
gg - more than one sternebra misaligned	1	1	0.7	0	0	-	4	3	2.1	0	0	-
hh - one sternebra assymmetric	0	0	-	1	1	0.5	0	0	-	0	0	-

NOTE: A foetus may appear in more than one category

# = group mean per litter  
NF = number of foetuses in category  
NL = number of litters in category

TABLE 10 (contd)  
GROUP INCIDENCE OF FOETAL SKELETAL FINDINGS

Skeletal Findings	Number of Foetuses Examined						Dose Level mg/kg		
	0			12.5			62.5		
	174	175	159	182					
NF	NL	%#	NF	NL	%#	NF	NL	%#	NF
Total Number Affected	72	22	40.3	98	23	53.3	86	22	51.3
									23
									69.5

Vertebral

ii - one thoracic vertebral centrum semi-bipartite      10    6    5.6    14    7    7.3    18    9    9.7    30\*\* 14    16.4  
 jj - more than one thoracic vertebral centrum semi-bipartite      2    1    1.2    3    3    1.5    5    3    2.8    4    4    2.2  
 kk - one thoracic vertebral centrum bipartite      0    0    -    3    3    1.5    0    0    -    0    0    -  
 ll - more than one thoracic vertebral centrum bipartite      0    0    -    1    1    0.5    0    0    -    0    0    -  
 mm - atlases short      0    0    -    1    1    0.5    0    0    -    0    0    -  
 nn - Bilateral incomplete ossification of lumbar arches      0    0    -    0    0    -    0    0    -    1    1    0.5

NOTE: A foetus may appear in more than one category  
 \*\* = significantly different from control ( $p < 0.01$ )

# = group mean per litter  
 NF = number of foetuses in category  
 NL = number of litters in category

TABLE 10 (contd)  
GROUP INCIDENCE OF FOETAL SKELETAL FINDINGS

Skeletal Findings	Dose Level mg/kg						
	Number of Foetuses Examined						
	0	12.5	62.5	125			
NF	NL	%#	NF	NL	%#	NF	NL
Total Number Affected	72	22	40.3	98	23	53.3	86
						22	51.3
						124	23
						69.5	

Pelvic Girdle

oo - incomplete ossification of pubis(es)	6	4	3.8	2	2	1.1	5	4	3.5			
pp - irregular ossification of pubis(es)	0	0	-	c	0	-	2	1	1.0	3	1	1.4
qq - no ossification of pubes	1	1	0.6	1	1	0.5	3	2	3.3	0	0	-
rr - small/short pubes	1	1	0.6	3	1	1.4	0	0	-	1	1	0.5
ss - incomplete ossification of ischium(a)	0	0	-	2	2	1.0	0	0	-	2	1	1.1
tt - no ossification of ischia	0	0	-	0	0	-	1	1	2.1	0	0	-
uu - short ischium	0	0	-	0	0	-	1	1	0.6	0	0	-
vv - incomplete ossification of illia	0	0	-	0	0	-	1	1	2.1	0	0	-
ww - pelvic shift (27 pre sacral vertebrae)	0	0	-	1	1	0.5	0	0	-	0	0	-

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NOTE: A foetus may appear in more than one category

# = group mean per litter  
NF = number of foetuses in category  
NL = number of litters in category

TABLE 10 (contd) GROUP INCIDENCE OF FOETAL SKELETAL FINDINGS

		Dose Level mg/kg					
		Number of Foetuses Examined					
		0	12.5	62.5	125		
<b>Skeletal Findings</b>							
NF	NL	%#	NF	NL	%#	NF	NL
174			175			159	
							182
Total Number Affected	72	22	40.3	98	23	53.3	86
						22	51.3
						124	23
						69.5	

Hind Limbs

xx - no ossification of femurs

yy - incomplete ossification of tibiae and fibulae

NOTE: A foetus may appear in more than one category

# = group mean per litter  
NF = number of foetuses in category  
NL = number of litters in category



A P P E N D I C E S

## APPENDIX I

IPPD : ORAL GAVAGE TERATOLOGY STUDY IN THE RAT  
INDIVIDUAL ADULT CLINICAL SIGNS AND NECROPSY FINDINGS

GROUP: 3

Dam Number	Status	Clinical Signs (Onset and Final Duration)		Necropsy Finding
			Days Post Coitum	
53	TK	No abnormalities detected		Intrauterine haemorrhage (R horn)
64	TK	Noisy respiration (7-8)		NAD

TK = terminal kill

NAD = no abnormalities detected

## APPENDIX I

IPPD : ORAL GAVAGE TERATOLOGY STUDY IN THE RAT  
INDIVIDUAL ADULT CLINICAL SIGNS AND NECROPSY FINDINGS

GROUP: 4

DOSE LEVEL (mg/kg): 125

Dam Number	Status	Clinical Signs (Onset and Final Duration)		Necropsy Finding
		Days	Post Coitum	
73	TK	NAD		Left kidney - increased renal pelvic cavitation
74	TK	Salivation immediately before dosing (12-13)		NAD
75	TK	Salivation immediately before dosing (10,12)		NAD
76	TK	Salivation immediately before dosing (10,12-13)		NAD
77	TK	Salivation immediately before dosing (11,12)		NAD
78	TK	Salivation immediately before dosing (11-12,14)		NAD
82	TK	NAD		Left lobe of Liver - 3 white foci approximately 1 mm x 1 mm
88	TK	Salivation immediately before dosing (13)		NAD
91	TK	Salivation immediately before dosing (14-15)		NAD
92	TK	Faeces - soft and dark (15-16)		NAD
93	TK	Salivation immediately before dosing (14)		NAD
94	TK	Faeces - soft and dark (15)		NAD
95	TK	Faeces - soft and dark (13-16)		NAD
96	TK	Salivation immediately before dosing (11)		NAD
		Faeces - soft and dark (11-15)		NAD

TK = terminal kill

NAD = no abnormalities detected

## APPENDIX III

IPPD : ORAL GAVAGE TERATOLOGY STUDY IN THE RAT  
INDIVIDUAL BODYWEIGHTS (g) OF FEMALES POST COITUM

GROUP: 1

DOSE LEVEL (mg/kg): 0

Animal Number	Day Post Coitum													
	0	3	6	7	8	9	10	11	12	13	14	15	18	20
1	273	276	303	313	320	321	328	333	349	343	353	387	423	
2	256	273	289	294	295	303	312	318	321	332	335	344	389	426
3	256	272	287	288	298	307	319	322	326	340	348	356	409	456
4	249	264	282	289	296	301	308	312	323	328	341	346	399	441
5	280	289	306	306	322	329	336	339	347	356	363	372	409	449
6	281	298	310	311	317	323	329	336	343	352	354	360	404	432
7	245	256	265	269	274	280	285	294	294	301	309	316	345	382
8	265	289	300	301	311	322	330	328	333	341	344	351	380	388
9	260	276	294	300	309	316	320	328	339	346	349	363	410	447
10	278	299	318	320	330	335	349	361	375	379	390	398	452	488
11	249	267	275	277	280	289	296	304	309	316	322	326	360	375
12	266	274	282	289	294	301	312	318	323	331	339	349	402	434

**APPENDIX II**  
**(continued)**

**IPPD : ORAL GAVAGE TERATOLOGY STUDY IN THE RAT**  
**INDIVIDUAL BODYWEIGHTS (g) OF FEMALES POST COITUM**

**GROUP: 1**

**DOSE LEVEL (mg/kg): 0**

<b>Animal Number</b>	Day Post Coitum									
	0	3	6	7	8	9	10	11	12	13
13	248	255	266	273	273	280	293	299	310	321
14	278	297	313	323	325	332	336	348	353	362
15	264	269	281	291	290	294	305	319	325	327
16	244	257	277	282	294	295	307	314	323	324
17	283	292	314	320	327	335	340	347	357	356
18	284	310	333	339	344	319	332	345	348	356
19	280	295	307	320	324	326	331	335	338	344
20	268	286	301	299	306	311	316	322	330	344
21	258	274	290	294	306	308	311	321	332	340
22	302	324	340	349	357	363	366	371	382	389
23	306	331	351	360	364	362	370	377	388	390
24	276	300	314	312	321	333	332	335	347	355

**APPENDIX II**  
**(continued)**

**IPPD : ORAL GAVAGE TERATOLOGY STUDY IN THE RAT**  
**INDIVIDUAL BODYWEIGHTS (g) OF FEMALES POST COITUM**

**GROUP: 2**      **DOSE LEVEL (mg/kg): 12.5**

Animal Number	Day Post Coitum													
	0	3	6	7	8	9	10	11	12	13	14	15	18	20
25	244	258	277	279	285	293	303	307	312	319	328	340	372	397
26	270	274	287	287	294	308	320	317	322	343	346	359	405	442
27	254	268	282	285	286	294	301	306	310	326	337	347	382	411
28	260	281	299	300	302	314	320	327	332	352	355	370	426	455
29	268	292	306	308	320	324	329	336	346	351	362	364	398	426
30	263	284	298	304	312	320	328	335	340	338	345	351	400	435
31	266	292	295	304	314	326	333	338	351	360	370	379	414	449
32	245	273	278	285	291	293	303	310	312	318	331	337	385	413
33	288	306	321	330	339	356	363	375	382	388	394	408	460	506
34	276	284	301	308	307	312	325	335	340	345	350	367	392	414
35	272	294	313	315	322	329	336	351	355	365	379	382	421	445
36	253	270	287	298	288	306	306	321	329	332	345	347	388	420

**APPENDIX III**  
 (continued)

**IPPD : ORAL GAVAGE TERATOLOGY STUDY IN THE RAT**  
**INDIVIDUAL BODYWEIGHTS (g) OF FEMALES POST COITUM**

**GROUP: 2**      **DOSE LEVEL (mg/kg): 12.5**

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PROJECT NUMBER: 543/2

Animal Number	Day Post Coitum													
	0	3	6	7	8	9	10	11	12	13	14	15	18	
37	293	308	316	323	321	331	338	345	356	356	369	376	424	453
38	262	277	290	294	290	299	311	324	332	336	344	353	394	434
39	278	292	306	305	311	318	331	335	342	353	357	356	406	439
40	274	290	300	306	315	320	336	345	347	361	367	369	418	457
41	268	277	299	305	308	318	329	331	342	350	364	370	417	442
42	278	290	311	307	319	322	328	342	344	359	365	367	413	449
43	271	279	294	286	294	303	308	311	320	326	330	336	366	383
44	294	313	324	321	331	339	346	354	362	373	381	390	442	478
45	292	314	311	315	323	330	335	339	351	357	364	379	423	453
46	260	283	283	290	297	301	307	309	316	322	328	336	382	425
47	262	272	285	287	295	298	303	309	315	316	321	327	368	388
48	293	316	328	333	335	342	346	357	363	365	371	378	417	457

**APPENDIX III**  
(continued)

**IPPD : ORAL GAVAGE TERATOLOGY STUDY IN THE RAT**  
**INDIVIDUAL BODYWEIGHTS (g) OF FEMALES POST COITUM**

**GROUP: 3**

**DOSE LEVEL (mg/kg): 62.5**

Animal Number	Day Post Coitum													
	0	3	6	7	8	9	10	11	12	13	14	15	18	20
49	245	253	269	273	278	287	292	301	310	314	325	337	368	402
50	253	268	291	296	301	303	308	316	322	334	336	348	374	395
51	260	270	296	302	308	311	324	335	339	350	360	373	416	456
52	267	283	292	297	309	309	322	326	332	343	353	364	410	438
53	263	279	293	293	298	302	313	320	325	336	344	355	388	420
54	267	276	278	290	295	301	311	318	325	329	343	352	396	427
55	277	293	307	318	315	330	338	348	355	365	375	385	430	465
56	271	287	296	302	311	320	324	337	342	351	357	363	407	426
57	223	250	264	253	250	266	271	272	285	293	298	307	336	354
58	259	275	301	303	301	306	313	321	331	332	342	351	402	444
59	273	290	303	309	317	330	327	340	346	351	360	370	403	438
60	272	290	301	303	314	321	324	336	346	349	361	373	421	444

**APPENDIX III**  
**(continued)**

**IPPD : ORAL GAVAGE TERATOLOGY STUDY IN THE RAT**  
**INDIVIDUAL BODYWEIGHTS (g) OF FEMALES POST COITUM**

**GROUP: 3**

**DOSE LEVEL (mg/kg): 62.5**

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**PROJECT NUMBER: 543/2**

Animal Number	Day Post Coitum													
	0	3	6	7	8	9	10	11	12	13	14	15	18	20
61	293	301	317	325	330	339	341	350	362	377	382	419	442	
62	256	277	289	298	306	312	311	317	335	338	355	360	405	441
63	278	292	305	312	320	327	332	343	349	360	361	369	411	448
64	278	295	310	291	301	314	322	333	339	350	355	356	380	394
65	255	260	275	293	290	293	295	305	318	324	337	344	370	393
66	281	296	324	318	332	329	343	360	361	371	380	394	445	482
67	282	282	295	289	299	303	310	311	319	325	335	367	393	
68	274	296	310	308	315	323	328	336	344	352	361	370	408	438
69	288	309	329	328	336	343	349	354	371	378	384	394	435	465
70	281	305	301	306	314	311	315	322	336	335	348	357	407	443
71	259	274	285	281	290	298	305	310	313	319	329	334	375	400
72	311	335	355	351	356	361	373	377	387	398	404	413	462	493

**A P P E N D I X**  
**(continued)**

**IPPD : ORAL GAVAGE TERATOLOGY STUDY IN THE RAT**  
**INDIVIDUAL BODYWEIGHTS (g) OF FEMALES POST COITUM**

**GROUP: 4**

**DOSE LEVEL (mg/kg): 125**

Animal Number	Day Post Coitum									
	0	3	6	7	8	9	10	11	12	13
73	270	284	308	308	312	318	337	350	352	367
74	256	277	298	300	306	311	325	329	331	344
76	257	269	288	292	297	304	307	317	324	329
77	274	298	307	314	321	319	331	342	356	365
78	234	255	268	272	283	284	291	300	308	309
79	252	264	268	274	281	280	295	301	311	323
80	265	290	302	308	319	301	306	339	344	353
81	256	278	288	296	310	328	335	332	343	357
82	252	267	284	290	292	297	310	319	332	338
83	270	288	309	307	307	314	329	349	356	361
84	238	254	265	264	271	282	295	306	310	319
Not pregnant 75										
	244	252	272	277	282	289	288	294	300	289
										286
										281
										278
										291

**APPENDIX III**  
**(continued)**

IPPD : ORAL GAVAGE TERATOLOGY STUDY IN THE RAT

**INDIVIDUAL BODYWEIGHTS (g) OF FEMALES POST COITUM**

**GROUP: 4**

**DOSE LEVEL (mg/kg): 125**

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PROJECT NUMBER: 543/2

Animal Number	Day Post Coitum													
	0	3	6	7	8	9	10	11	12	13	14	15	18	20
85	277	292	305	303	306	314	321	324	336	348	361	364	422	456
86	278	290	299	311	313	322	334	334	344	349	360	360	403	433
87	263	279	297	305	306	315	328	336	340	352	361	371	405	434
88	271	286	295	308	319	319	330	338	343	354	358	362	409	451
89	283	290	314	316	343	358	360	368	389	390	402	410	447	459
90	245	258	289	280	293	295	297	317	314	316	324	332	359	369
91	272	282	298	297	290	291	295	306	309	320	319	325	351	376
92	269	287	306	304	310	319	324	328	329	351	355	362	411	432
93	295	315	327	326	341	340	350	349	363	365	374	384	418	429
94	258	274	284	291	306	310	312	328	339	351	360	396	417	
95	278	292	308	316	320	321	333	339	347	359	366	371	413	436
96	286	307	327	324	328	334	343	351	361	360	364	376	409	436

## APPENDIX III

IPPD : ORAL GAVAGE TERATOLOGY STUDY IN THE RAT  
INDIVIDUAL BODYWEIGHT CHANGE OF FEMALES POST COITUM\*

GROUP: 1

Animal Number	Day Post Coitum												DOSE LEVEL (mg/kg): 0	
	0	3	6	7	8	9	10	11	12	13	14	15	18	
1	-30	-27	*	10	10	17	18	25	30	46	40	50	84	120
2	-33	-16	*	5	6	14	23	29	32	43	46	55	100	137
3	-31	-15	*	1	11	20	32	35	39	53	61	69	122	169
4	-33	-18	*	7	14	19	26	30	41	46	59	64	117	159
5	-26	-17	*	0	16	23	30	33	41	50	57	66	103	143
6	-29	-12	*	1	7	13	19	26	33	42	44	50	94	122
7	-20	-9	*	4	9	15	20	29	29	36	44	51	80	117
8	-35	-11	*	1	11	22	30	28	33	41	44	51	80	88
9	-34	-18	*	6	15	22	26	34	45	52	55	69	116	153
10	-40	-19	*	2	12	17	31	43	57	61	72	80	134	170
11	-26	-8	*	2	5	14	21	29	34	41	47	51	85	100
12	-16	-8	*	7	12	19	30	36	41	49	57	67	120	152

\* = bodyweight change relative to day 6 post coitum

**APPENDIX III**  
**(continued)**

**GROUP: 1**

**IPPD : ORAL GAVAGE TERATOLOGY STUDY IN THE RAT**  
**INDIVIDUAL BODYWEIGHT CHANGE OF FEMALES POST COITUM\***

Animal Number	Day Post Coitum										DOSE LEVEL (mg/kg): 0
	0	3	6	7	8	9	10	11	12	13	
13	-18	-11	*	7	7	14	27	33	44	44	55
14	-35	-16	*	10	12	19	23	35	40	40	49
15	-17	-12	*	10	9	13	24	38	44	46	60
16	-33	-20	*	5	17	18	30	37	46	47	50
17	-31	-22	*	6	13	21	26	33	43	42	51
18	-49	-23	*	6	11	-14	-1	12	15	23	35
19	-27	-12	*	13	17	19	24	28	31	37	46
20	-33	-15	*	-2	5	10	15	21	29	43	44
21	-32	-16	*	4	16	18	21	31	42	50	48
22	-38	-16	*	9	17	23	26	31	42	49	56
23	-45	-20	*	9	13	11	19	26	37	39	49
24	-38	-14	*	-2	7	19	18	21	33	41	48

\* = bodyweight change relative to day 6 post coitum

**APPENDIX III**  
**(continued)**

**IPPD : ORAL GAVAGE TERATOLOGY STUDY IN THE RAT**  
**INDIVIDUAL BODYWEIGHT CHANGE OF FEMALES POST COITUM\***

**GROUP: 2**

**DOSE LEVEL (mg/kg): 12.5**

Animal Number	Day Post Coitum									
	0	3	6	7	8	9	10	11	12	13
25	-33	-19	*	2	8	16	26	30	35	42
26	-17	-13	*	0	7	21	33	30	35	56
27	-28	-14	*	3	4	12	19	24	28	44
28	-39	-18	*	1	3	15	21	28	33	53
29	-38	-14	*	2	14	18	23	30	40	45
30	-35	-14	*	6	14	22	30	37	42	40
31	-29	-3	*	9	19	31	38	43	56	65
32	-33	-5	*	7	13	15	25	32	34	40
33	-33	-15	*	9	18	35	42	54	61	67
34	-25	-17	*	7	6	11	24	34	39	44
35	-41	-19	*	2	9	16	23	38	42	52
36	-34	-17	*	11	1	19	19	34	42	45

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**PROJECT NUMBER: 543/2**

\* = bodyweight change relative to day 6 post coitum

**APPENDIX III**  
**(continued)**

**IPPD : ORAL GAVAGE TERATOLOGY STUDY IN THE RAT**  
**INDIVIDUAL BODYWEIGHT CHANGE OF FEMALES POST COITUM\***

**GROUP: 2**

**DOSE LEVEL (mg/kg): 12.5**

Animal Number	Day Post Coitum									
	0	3	6	7	8	9	10	11	12	13
37	-23	-8	*	7	5	15	22	29	40	40
38	-28	-13	*	4	0	9	21	34	42	46
39	-28	-14	*	-1	5	12	25	29	36	47
40	-26	-10	*	6	15	20	36	45	47	61
41	-31	-22	*	6	9	19	30	32	43	51
42	-33	-21	*	-4	8	11	17	31	33	48
43	-23	-15	*	-8	0	9	14	17	26	32
44	-30	-11	*	-3	7	15	22	30	38	49
45	-19	3	*	4	12	19	24	28	40	46
46	-23	0	*	7	14	18	24	26	33	39
47	-23	-13	*	2	10	13	18	24	30	31
48	-35	-12	*	5	7	14	18	29	35	37

**PROJECT NUMBER: 543/2**

\* = bodyweight change relative to day 6 post coitum

**APPENDIX III**  
**(continued)**

**GROUP: 3**

**IPPD : ORAL GAVAGE TERATOLOGY STUDY IN THE RAT**  
**INDIVIDUAL BODYWEIGHT CHANGE OF FEMALES POST COITUM\***

Animal Number	Day Post Coitum										DOSE LEVEL (mg/kg): 62.5			
	0	3	6	7	8	9	10	11	12	13				
49	-24	-16	*	4	9	18	23	32	41	45	56	68	99	133
50	-38	-23	*	5	10	12	17	25	31	43	45	57	83	104
51	-36	-26	*	6	12	15	28	39	43	54	64	77	120	160
52	-25	-9	*	5	17	17	30	34	40	51	61	72	118	146
53	-30	-14	*	0	5	9	20	27	32	43	51	62	95	127
54	-11	-2	*	12	17	23	33	40	47	51	65	74	118	149
55	-30	-14	*	11	8	23	31	41	48	58	68	78	123	158
56	-25	-9	*	6	15	24	28	41	46	55	61	67	111	130
57	-41	-14	*	-11	-14	2	7	8	21	29	34	43	72	90
58	-42	-26	*	2	0	5	12	20	30	31	41	50	101	143
59	-30	-13	*	6	14	27	24	37	43	48	57	67	100	135
60	-29	-11	*	2	13	20	23	35	45	48	60	72	120	143

\* = bodyweight change relative to day 6 post coitum

APPENDIX III  
(continued)

GROUP: 3

IPPD : ORAL GAVAGE TERATOLOGY STUDY IN THE RAT  
INDIVIDUAL BODYWEIGHT CHANGE OF FEMALES POST COITUM\*

Animal Number	Day Post Coitum										DOSE LEVEL (mg/kg): 62.5			
	0	3	6	7	8	9	10	11	12	13	14			
61	-24	-16	*	8	13	22	24	33	45	45	60	65	102	125
62	-33	-12	*	9	17	23	22	28	46	49	66	71	116	152
63	-27	-13	*	7	15	22	27	38	44	55	56	64	106	143
64	-32	-15	*	-19	-9	4	12	23	29	40	45	46	70	84
65	-20	-15	*	18	15	18	20	30	43	49	62	69	95	118
66	-43	-28	*	-6	8	5	19	36	37	47	56	70	121	158
67	-13	-13	*	-6	4	8	15	16	24	24	30	40	72	98
68	-36	-14	*	-2	5	13	18	26	34	42	51	60	98	128
69	-41	-20	*	-1	7	14	20	25	42	49	55	65	106	136
70	-20	4	*	5	13	10	14	21	35	34	47	56	106	142
71	-26	-11	*	-4	5	13	20	25	28	34	44	49	90	115
72	-44	-20	*	-4	1	6	18	22	32	43	49	58	107	138

\* = bodyweight change relative to day 6 post coitum

**APPENDIX III**  
(continued)

**GROUP: 4**

**IPPO : ORAL GAVAGE TERATOLOGY STUDY IN THE RAT**  
**INDIVIDUAL BODYWEIGHT CHANGE OF FEMALES POST COITUM\***

**DOSE LEVEL (mg/kg): 125**

Animal Number	Day Post Coitum												15	18	20
	0	3	6	7	8	9	10	11	12	13	14	71			
73	-38	-24	*	0	4	10	29	42	44	59	64	71	121	151	
74	-42	-21	*	2	8	13	27	31	33	46	55	65	114	145	
76	-31	-19	*	4	9	16	19	29	36	41	53	60	100	119	
77	-33	-9	*	7	14	12	24	35	49	58	69	85	132	165	
78	-34	-13	*	4	15	16	23	32	40	41	50	58	98	128	
79	-16	-4	*	6	13	12	27	33	43	55	62	63	117	157	
80	-37	-12	*	6	17	-1	4	37	42	51	59	70	106	157	
81	-32	-10	*	8	22	40	47	44	55	69	72	86	121	174	
82	-32	-17	*	6	8	13	26	35	48	54	67	75	113	140	
83	-39	-21	*	-2	-2	5	20	40	47	52	65	59	120	146	
84	-27	-11	*	0	-1	6	17	30	41	45	54	59	94	126	
Not pregnant 75	-28	-20	*	5	10	17	16	22	28	17	14	9	6	19	

\* = bodyweight change relative to day 6 post coitum

APPENDIX III  
(continued)

GROUP: 4

IPPD : ORAL GAVAGE TERATOLOGY STUDY IN THE RAT  
INDIVIDUAL BODYWEIGHT CHANGE OF FEMALES POST COITUM\*

Animal Number	Day Post Coitum										DOSE LEVEL (mg/kg): 125			
	0	3	6	7	8	9	10	11	12	13				
85	-28	-13	*	-2	1	9	16	19	31	43	56	59	117	151
86	-21	-9	*	12	14	23	35	45	50	50	61	61	104	134
87	-34	-18	*	8	9	18	31	39	43	55	64	74	108	137
88	-24	-9	*	13	24	24	35	43	48	59	63	67	114	156
89	-31	-24	*	2	29	44	46	54	75	76	88	96	133	145
90	-44	-31	*	-9	4	6	8	28	25	27	35	43	70	80
91	-26	-16	*	-1	-8	-7	-3	8	11	22	21	27	53	78
92	-37	-19	*	-2	4	13	18	22	23	45	49	56	105	126
93	-32	-12	*	-1	14	13	23	22	36	38	47	57	91	102
94	-26	-10	*	7	22	22	26	28	44	55	67	76	112	133
95	-30	-16	*	8	12	13	25	31	39	51	58	63	105	128
95	-41	-20	*	-3	1	7	16	24	34	33	37	49	82	109

\* = bodyweight change relative to day 6 post coitum

**APPENDIX IV**

**IPPD : ORAL GAVAGE TERATOLOGY STUDY IN THE RAT**  
**INDIVIDUAL FOOD CONSUMPTION (g/RAT/DAY) OF FEMALES POST COITUM**

**GROUP: 1**

Animal Number	Days Post Coitum						
	0-3	3-6	6-9	9-12	12-15	15-18	18-20
1	21.7	28.7	28.7	31.0	31.0	33.3	32.5
2	23.7	25.7	26.7	28.3	31.7	34.0	33.5
3	22.0	24.7	27.3	30.0	31.7	38.7	35.0
4	26.0	28.0	28.7	30.7	33.0	36.3	33.5
5	22.7	30.3	30.0	36.3	35.0	36.7	38.5
6	26.7	29.0	28.3	31.0	33.0	37.7	37.0
7	22.7	25.3	25.0	26.0	27.0	28.0	29.5
8	26.7	26.3	25.7	26.3	31.0	33.0	29.0
9	27.7	31.7	33.3	36.0	37.0	38.3	37.5
10	27.3	29.3	29.3	34.3	34.7	38.7	35.5
11	23.7	24.0	24.0	30.3	32.7	36.7	34.0
12	24.3	27.7	28.0	31.7	35.3	37.3	36.5

**APPENDIX IV**  
**INDIVIDUAL FOOD CONSUMPTION (g/RAT/DAY) OF FEMALES POST COITUM**  
 (continued)

**IPPD : ORAL GAVAGE TERATOLOGY STUDY IN THE RAT**

**GROUP: 1**

Animal Number	Days Post Coitum						DOSE LEVEL (mg/kg): 0
	0-3	3-6	6-9	9-12	12-15	15-18	
13	22.0	23.3	23.0	26.0	28.7	34.7	35.5
14	27.0	31.3	27.7	33.3	32.3	37.7	37.0
15	23.3	24.3	25.0	29.7	31.0	34.3	33.0
16	21.0	26.0	25.0	30.0	27.3	32.7	32.5
17	23.3	27.3	28.3	29.3	31.7	34.7	34.5
18	29.3	33.7	29.3	28.7	34.0	34.3	33.5
19	26.7	27.3	28.7	30.3	31.3	34.7	31.0
20	23.7	24.7	24.0	27.0	30.3	34.3	35.5
21	23.0	28.0	26.7	30.7	31.0	32.7	32.5
22	25.0	30.0	32.3	34.7	34.0	36.7	31.5
23	29.0	32.3	31.0	34.3	36.3	38.0	35.0
24	25.0	28.0	28.7	30.0	33.7	34.7	34.0

APPENDIX IV  
(continued)

INDIVIDUAL FOOD CONSUMPTION (g/RAT/DAY) OF FEMALES POST COITUM

Animal Number	Days Post Coitum						DOSE LEVEL (mg/kg): 12.5
	0-3	3-6	6-9	9-12	12-15	15-18	
25	23.7	26.7	26.7	30.3	33.0	32.7	31.5
26	21.0	24.0	24.3	28.3	32.0	37.7	33.5
27	21.7	24.3	24.0	27.3	34.0	34.7	30.0
28	25.0	27.7	27.7	33.0	35.7	41.7	36.5
29	27.0	29.7	30.3	32.3	34.7	36.3	33.5
30	26.3	30.7	30.3	32.3	29.7	34.3	33.0
31	29.0	29.7	31.3	34.3	40.7	41.3	41.0
32	23.7	26.0	25.3	27.7	29.7	33.3	31.5
33	26.7	30.3	30.7	35.7	35.3	33.0	42.5
34	25.3	26.3	27.0	28.0	32.3	34.7	31.5
35	27.7	29.7	29.7	32.0	37.3	36.0	35.5
36	23.3	24.7	24.3	27.0	29.3	33.3	30.0

**APPENDIX IV**  
**(continued)**

**IPPD : ORAL GAVAGE TERATOLOGY STUDY IN THE RAT**  
**INDIVIDUAL FOOD CONSUMPTION (g/RAT/DAY) OF FEMALES POST COITUM**

**GROUP: 2**

Animal Number	Days Post Coitum						<b>DOSE LEVEL (mg/kg): 12.5</b>
	0-3	3-6	6-9	9-12	12-15	15-18	
37	25.3	26.7	27.3	28.0	30.0	33.7	33.0
38	23.0	24.7	23.3	29.3	29.7	33.3	32.5
39	25.0	26.3	25.0	27.3	28.3	32.3	29.5
40	25.7	25.7	26.7	30.3	32.0	36.3	33.0
41	26.0	30.0	31.3	33.7	35.7	37.7	32.0
42	27.0	32.0	31.3	32.7	33.0	36.7	35.0
43	21.0	22.3	21.3	25.0	27.3	28.7	29.5
44	26.3	26.3	27.7	32.3	34.0	36.3	33.5
45	21.7	31.0	27.3	33.7	34.7	38.0	35.5
46	22.0	27.7	24.3	29.0	28.7	35.0	40.5
47	20.3	22.0	22.7	25.0	24.7	29.7	26.5
48	26.3	28.0	30.3	29.3	31.3	33.7	34.0

**APPENDIX IV**  
**(continued)**

**IPPD : ORAL GAVAGE TERATOLOGY STUDY IN THE RAT**  
**INDIVIDUAL FOOD CONSUMPTION (g/RAT/DAY) OF FEMALES POST COITUM**

GROUP: 3	Animal Number	DOSE LEVEL (mg/kg): 62.5					
		0-3	3-6	6-9	9-12	12-15	15-18
Days Post Coitum							
49		18.3	24.7	24.3	26.0	31.3	33.0
50		22.3	28.3	27.3	25.3	32.3	35.7
51		21.0	28.7	27.0	30.3	35.0	37.3
52		21.7	23.7	22.7	29.7	31.3	35.3
53		21.3	27.7	24.0	27.0	31.3	33.7
54		25.3	25.0	27.0	28.7	32.3	35.3
55		23.7	30.3	26.0	33.3	35.0	37.7
56		27.3	29.7	29.3	34.7	34.0	38.3
57		22.3	28.0	18.3	23.7	27.7	30.7
58		23.3	32.0	23.3	32.3	32.3	37.3
59		29.3	27.7	28.3	28.3	32.0	33.3
60		27.3	28.3	26.0	32.3	35.0	40.7

APPENDIX IV  
(continued)

IPPO : ORAL GAVAGE TERATOLOGY STUDY IN THE RAT  
INDIVIDUAL FOOD CONSUMPTION (g/RAT/DAY) OF FEMALES POST COITUM

Animal Number	Days Post Coitum						
	0-3	3-6	6-9	9-12	12-15	15-18	18-20
61	27.7	31.3	27.3	30.0	30.7	34.0	36.0
62	28.0	26.7	23.3	28.3	31.3	38.0	38.0
63	25.0	26.7	24.3	28.7	29.7	36.3	39.5
64	28.7	27.3	17.7	31.0	31.7	35.3	34.5
65	19.0	21.7	22.7	22.7	28.7	29.7	30.0
66	28.7	31.3	29.7	32.3	37.3	41.3	39.5
67	21.3	23.7	22.7	26.0	27.7	32.7	32.5
68	26.3	28.0	25.7	30.7	29.3	35.3	37.0
69	22.3	30.0	25.7	30.0	33.3	36.3	39.5
70	20.7	25.3	22.0	27.7	28.0	31.7	34.5
71	24.0	24.7	23.3	26.7	28.7	33.0	33.5
72	28.3	31.0	31.3	32.3	35.0	41.3	39.5

**APPENDIX IV**  
**(continued)**

**IPPD : ORAL GAVAGE TERATOLOGY STUDY IN THE RAT**  
**INDIVIDUAL FOOD CONSUMPTION (g/RAT/DAY) OF FEMALES POST COITUM**

**GROUP: 4**

**DOSE LEVEL (mg/kg): 125**

Animal Number	Days Post Coitum						
	0-3	3-6	6-9	9-12	12-15	15-18	18-20
73	20.0	31.3	24.3	34.7	36.3	40.3	40.0
74	22.7	26.7	28.3	31.7	35.3	38.0	37.5
76	25.7	26.7	26.3	27.0	30.7	32.0	32.5
77	26.3	27.0	26.3	30.3	34.3	39.3	40.5
78	23.3	26.7	24.7	27.7	29.7	35.0	35.0
79	23.7	25.0	23.0	27.3	31.0	34.0	35.5
80	27.3	29.0	23.3	29.7	32.3	36.0	37.5
81	25.7	20.7	29.3	31.0	33.7	38.0	41.5
82	26.0	27.3	21.3	30.7	31.7	33.7	33.5
83	26.0	30.0	21.7	34.7	31.3	33.3	32.5
84	21.0	25.3	15.0	32.7	30.7	32.3	33.0
Not Pregnant 75	21.7	24.0	24.3	21.7	20.7	20.7	26.5

APPENDIX IV INDIVIDUAL FOOD CONSUMPTION (g/RAT/DAY) OF FEMALES POST COITUM  
(continued)

Animal Number	Days Post Coitum						
	0-3	3-6	6-9	9-12	12-15	15-18	18-20
85	26.0	27.7	18.7	32.0	35.0	34.3	34.0
86	25.0	26.0	19.7	31.3	32.7	34.3	36.5
87	23.0	27.3	24.7	28.3	32.0	34.0	34.0
88	28.3	28.7	26.3	29.3	33.0	37.7	39.5
89	28.0	31.3	30.3	38.7	39.7	38.7	38.0
90	20.0	23.3	28.0	29.0	28.7	32.3	32.0
91	23.7	26.0	17.3	23.3	24.3	31.0	28.5
92	24.0	27.0	21.3	28.3	30.3	36.7	38.5
93	25.7	27.7	27.0	27.7	31.0	35.7	36.0
94	20.0	26.0	21.7	27.0	32.7	35.7	33.5
95	24.0	28.3	25.3	30.7	33.3	36.3	37.0
96	23.7	28.0	23.0	29.3	32.3	35.7	34.5

APPENDIX V

INDIVIDUAL LITTER DATA

GROUP: 1

DOSE LEVEL (mg/kg): 0

IPPD : ORAL GAVAGE TERATOLOGY STUDY IN THE RAT

Animal Number	Number of corpora lutea	Number of Live Foetuses			%			Embryonic/Foetal Deaths			Implantation Loss %		Total Litter Height (g)	Mean Foetal Weight (g)
		Male		Total	Foetuses		Early	Late	Total	Pre	Post			
		Hale	Female											
1	18	7	8	15	46.7	2	0	2	5.6	11.8	51.3	3.42		
2	15	8	6	14	57.1	1	0	1	0.0	6.7	56.7	3.91		
3	20	8	12	20	40.0	0	0	0	0.0	0.0	71.2	3.56		
4	20	13	6	19	68.4	0	0	0	5.0	0.0	68.0	3.58		
5	16	11	3	14	78.6	0	0	0	12.5	0.0	51.4	3.67		
6	15	6	6	12	50.0	1	0	1	13.3	7.7	43.8	3.65		
7	15	6	7	13	46.2	0	0	0	13.3	0.0	51.8	3.99		
8	11	4	4	8	50.0	0	0	0	27.3	0.0	28.0	3.50		
9	17	10	4	14	71.4	2	0	2	5.9	12.5	52.3	3.74		
10	19	9	8	17	52.9	0	0	0	10.5	0.0	68.1	4.01		
11	13	4	3	7	57.1	0	0	0	46.2	0.0	26.9	3.85		
12	25	9	9	18	50.0	1	0	1	24.0	5.3	59.7	3.32		

IOPPD : ORAL GAVAGE TERATOLOGY STUDY IN THE RAT

APPENDIX V  
(continued)

INDIVIDUAL LITTER DATA

GROUP: 1

DOSE LEVEL (mg/kg): 0

Animal Number	Number of Corpora Lutea	Number of Live Foetuses			Male	Embryonic/Foetal Deaths			Implantation Loss %		Total Litter Weight (g)	Mean Foetal Weight (g)
		Male	Female	Total		Footases	Early	Late	Total	Pre	Post	
13	19	10	7	17	58.8	0	0	0	10.5	0.0	61.4	3.61
14	17	6	9	15	40.0	0	0	0	11.8	0.0	63.8	4.25
15	20	8	11	19	42.1	0	0	0	5.0	0.0	71.0	3.74
16	17	8	8	16	50.0	0	0	0	5.9	0.0	62.0	3.88
17	21	7	10	17	41.2	0	0	0	19.0	0.0	61.9	3.64
18	27	4	12	16	25.0	1	0	1	37.0	5.9	54.8	3.42
19	18	6	5	11	54.5	1	0	1	33.3	8.3	45.3	4.12
20	26	8	7	15	53.3	0	0	0	42.3	0.0	52.7	3.51
21	15	2	12	14	14.3	0	0	0	6.7	0.0	47.5	3.39
22	20	8	11	19	42.1	0	0	0	5.0	0.0	77.1	4.06
23	18	6	7	13	46.2	2	0	2	16.7	13.3	53.5	4.11
24	20	9	9	18	50.0	2	0	2	0.0	10.0	58.1	3.23

IPPD : ORAL GAVAGE TERATOLOGY STUDY IN THE RAT

APPENDIX  
(continued)

INDIVIDUAL LITTER DATA

GROUP: 2

DOSE LEVEL (mg/kg): 12.5

Animal Number	Number of Corpora Lutea	Number of Live Foetuses			X Foetuses	Embryonic/Foetal Deaths			Implantation Loss %		Total Litter Weight (g)	Mean Foetal Weight (g)
		H male	F female	Total		Early	Late	Total	Pre	Post		
25	13	4	6	10	40.0	0	0	0	23.1	0.0	52.2	5.22
26	19	7	10	17	41.2	2	0	2	0.0	10.5	71.0	4.18
27	16	6	7	13	46.2	1	0	1	12.5	7.1	48.8	3.75
28	16	10	6	16	62.5	0	0	0	0.0	0.0	92.4	5.77
29	17	5	4	9	55.6	1	0	1	41.2	10.0	33.8	3.76
30	16	6	9	15	40.0	1	0	1	0.0	6.3	62.4	4.16
31	18	8	9	17	47.1	1	0	1	0.0	5.6	58.8	3.46
32	25	10	5	15	66.7	0	0	0	40.0	0.0	54.0	3.60
33	22	8	9	17	47.1	1	0	1	18.2	5.6	61.3	3.60
34	21	2	7	9	22.2	0	0	0	57.1	0.0	33.7	3.74
35	18	4	10	14	28.6	4	0	4	0.0	22.2	52.5	3.75
36	18	9	6	15	60.0	0	0	0	16.7	0.0	55.8	3.72

IPPD : ORAL GAVAGE TERATOLOGY STUDY IN THE RAT

APPENDIX V  
(continued)

INDIVIDUAL LITTER DATA

GROUP: 2

DOSE LEVEL (mg/kg): 12.5

Animal Number	Number of corpora lutea	Number of Live Foetuses			%	Embryonic/Foetal Deaths			Implantation Loss %		Total Litter Weight (g)	Mean Foetal Weight (g)	
		Male		Female		Early		Late	Total	Pre	Post		
		Male	Female			Pre	Post			Pre	Post		
37	19	7	10	17	41.2	0	0	0	10.5	0.0	65.6	3.86	
38	17	10	6	16	62.5	0	0	0	5.9	0.0	58.9	4.31	
39	17	7	9	16	43.8	1	0	1	0.0	5.9	58.8	3.68	
40	18	7	11	18	38.9	0	0	0	0.0	0.0	69.4	3.85	
41	20	13	5	18	72.2	0	0	0	10.0	0.0	72.0	4.00	
42	20	10	9	19	52.6	0	0	0	5.0	0.0	68.7	3.62	
43	14	5	6	11	45.5	3	0	3	0.0	21.4	37.3	3.39	
44	22	11	9	20	55.0	0	0	0	9.1	0.0	76.6	3.83	
45	19	6	9	15	40.0	2	0	2	10.5	11.8	56.2	3.75	
46	19	9	7	16	56.3	0	0	0	15.8	0.0	60.2	3.76	
47	22	4	11	15	26.7	1	0	1	27.3	6.3	50.6	3.37	
48	18	10	6	16	62.5	2	0	2	0.0	11.1	60.4	3.78	

**A P P E N D I X V**  
 (continued)

**IPPD : ORAL GAVAGE TERATOLOGY STUDY IN THE RAT**

**INDIVIDUAL LITTER DATA**

**GROUP: 3**

**DOSE LEVEL (mg/kg): 62.5**

Animal Number	Number of Corpora Lutea	Number of Live Foetuses			% Foetuses	Embryonic/Foetal Deaths			Implantation Loss %		Total Litter Weight (g)	Mean Foetal Weight (g)
		Male	Female	Total		Early	Late	Total	Pre	Post		
49	17	10	5	15	66.7	1	0	1	5.9	6.3	57.4	3.83
50	13	2	3	5	40.0	4	0	4	30.8	44.4	17.9	3.57
51	16	9	6	15	60.0	1	0	1	0.0	6.3	79.5	5.30
52	20	9	7	16	56.3	0	0	0	20.0	0.0	66.4	4.15
53	17	9	6	15	60.0	1	0	1	5.9	6.3	50.2	3.34
54	18	12	5	17	70.6	0	0	0	5.6	0.0	62.8	3.69
55	24	10	11	21	47.6	0	0	0	12.5	0.0	73.8	3.51
56	16	8	4	12	66.7	1	0	1	18.8	7.7	45.3	3.78
57	19	2	5	7	28.6	2	0	2	52.6	22.2	25.8	3.68
58	27	7	6	15	46.7	1	0	1	40.7	6.3	52.1	3.48
59	21	6	7	13	46.2	1	0	1	33.3	7.1	44.8	3.44
60	23	5	9	14	35.7	1	0	1	34.8	6.7	56.8	4.06

**APPENDIX V**  
**(continued)**

**IIPPD : ORAL GAVAGE TERATOLOGY STUDY IN THE RAT**

**INDIVIDUAL LITTER DATA**

**GROUP: 3**

**DOSE LEVEL (mg/kg): 62.5**

Animal Number	Number of Corpora Lutea	Number of Live Foetuses			X			Embryonic/Foetal Deaths			Implantation Loss %			Total Litter Weight (g)	Mean Foetal Weight (g)		
		Hale	Female	Total	Hale	Foetuses	Total	Early	Late	Total	Pre	Post					
61	16	7	7	14	50.0	1	1	0	1	6.3	6.7	57.0	57.0	4.07			
62	20	7	7	14	50.0	1	1	0	1	25.0	6.7	54.5	54.5	3.90			
63	17	9	7	16	56.3	0	0	0	0	5.9	0.0	57.8	57.8	3.61			
64	8	0	3	3	0.0	0	0	0	0	62.5	0.0	11.2	11.2	3.73			
65	20	6	9	15	40.0	2	0	2	0	15.0	11.8	55.9	55.9	3.73			
66	24	5	13	18	27.8	0	0	0	0	25.0	0.0	75.4	75.4	4.19			
67	22	3	6	11	27.3	3	0	3	0	36.4	21.4	31.0	31.0	2.82			
68	16	8	6	14	57.1	2	0	2	0	0.0	12.5	57.6	57.6	4.11			
69	19	6	8	14	42.9	1	0	1	0	21.1	6.7	52.3	52.3	3.74			
70	19	7	11	18	38.9	0	0	0	0	5.3	0.0	70.0	70.0	3.89			
71	16	6	9	15	40.0	0	0	0	0	6.3	0.0	55.3	55.3	3.69			
72	18	10	5	15	66.7	0	0	0	0	16.7	0.0	59.4	59.4	3.96			

IPPD : ORAL GAVAGE TERATOLOGY STUDY IN THE RAT

APPENDIX  
(continued)

INDIVIDUAL LITTER DATA

GROUP: 4

DOSE LEVEL (mg/kg): 125

Animal Number	Number of Corpora Lutea	Number of Live Foetuses			Male Foetuses	Embryonic/Foetal Deaths			Implantation Loss %		Total Litter Weight (g)	Mean Foetal Weight (g)	
				Total		Early	Late	Total	Pre	Post			
		Male	Female										
73	19	10	8	18	55.6	1	0	1	0.0	5.3	67.0	3.72	
74	20	7	13	20	35.0	0	0	0	0.0	0.0	76.0	3.80	
75					Not Pregnant				5.6	5.9	65.8	4.11	
76	18	8	8	16	50.0	1	0	1	22.7	5.9	55.5	3.47	
77	22	5	11	16	31.3	1	0	1	6.7	0.0	53.2	3.80	
78	15	2	12	14	14.3	0	0	0	0.0	0.0	66.3	4.15	
79	17	6	10	16	37.5	0	1	1	0.0	17.4	0.0	72.1	3.80
80	23	7	12	19	36.8	0	0	0	10.0	0.0	73.0	4.06	
81	20	6	12	18	33.3	0	0	0	39.3	17.6	54.7	3.91	
82	28	9	5	14	64.3	3	0	3	1	1	62.6	4.17	
83	24	12	6	18	66.7	1	0	1	20.8	5.3	73.3	4.07	
84	17	10	5	15	66.7	1	0	1	5.9	6.3			

IOPD : ORAL GAVAGE TERATOLOGY STUDY IN THE RAT

APPENDIX V  
(continued)

INDIVIDUAL LITTER DATA

GROUP: 4

DOSE LEVEL (mg/kg): 125

Animal Number	Number of Corpora Lutea	Number of Live Foetuses			%			Embryonic/Foetal Deaths			Implantation Loss %		Total Litter Weight (g)	Mean Foetal Weight (g)
		Male		Total	Foetuses		Early	Late	Total	Pre	Post			
		Male	Female	Total										
85	22	3	15	18	16.7	0	0	0	0	18.2	0.0	74.4	4.13	
86	33	9	7	16	56.3	0	0	0	0	51.5	0.0	59.4	3.72	
87	19	7	8	15	46.7	0	0	0	0	21.1	0.0	60.2	4.01	
88	21	11	8	19	57.9	0	0	0	0	9.5	0.0	70.7	3.72	
89	26	11	10	21	52.4	1	0	1	1	15.4	4.5	76.7	3.65	
90	15	4	2	6	66.7	1	1	2	2	46.7	25.0	21.5	3.58	
91	14	4	6	10	40.0	0	0	0	0	28.6	0.0	40.5	4.05	
92	19	5	13	18	27.8	0	0	0	0	5.3	0.0	76.7	4.26	
93	16	5	9	14	35.7	0	0	0	0	12.5	0.0	48.1	3.43	
94	16	7	7	14	50.0	0	0	0	0	12.5	0.0	59.6	4.26	
95	19	10	9	19	52.6	0	0	0	0	0.0	0.0	64.2	3.38	
96	19	10	6	16	62.5	1	0	1	1	10.5	5.9	63.6	3.97	

APPENDIX VI

INDIVIDUAL CAESARIAN AND MACROSCOPIC FOETUS NECROPSY FINDINGS

KEY TO FOETAL FINDINGS

a = small foetus

b = pale foetus

c = reddened foetus

d = haemorrhage on hind foot

e = blood filled amniotic sac

f = encephalocele

g = haemorrhagic ring at base of tail

h = placenta enlarged and haemorrhagic

i = subcutaneous haemorrhage on head

j = blood in abdomen

**APPENDIX VI**  
**(contd)**  
**INDIVIDUAL CAESARIAN AND MACROSCOPIC FOETUS**  
**NECROPSY FINDINGS**

**GROUP: 1**

**DOSE LEVEL (mg/kg): 0**

Data Number	Parameter	Implantation Number												Right Horn of Uterus				
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	
	Implant Type*	V1	V2	V3	V4	V5	C	V6	V7	V8	ED	V9	V10	V11	V12	V13	V14	
	FWT (g)	3.33	3.31	3.51	3.61	3.09	3.50	3.36	3.55			3.65	3.64	3.82	3.32	3.59	2.65	3.38
1	Sex	F	F	F	H	F	H	F	F	H	H	H	H	H	F	H		
	Findings															a,b		
	Implant Type*	17																
1	FWT (g)		ED															
	Sex																	
	Findings																	
	Implant Type*	V1	V2	ED	V3	V4	V5	C	V6	V7	V8	V9	V10	V11	V12	V13	V14	
	FWT (g)	4.12	42.9		3.71	3.79	4.11	4.11	3.93	3.70	4.11	3.69	3.92	3.66	3.72	3.72	3.88	
2	Sex	H	H	F	H	F	H	H	F	F	H	H	H	F	F	H		
	Findings																	
	Implant Type*	V1	V2	V3	V4	V5	V6	V7	V8	C	V9	V10	V11	V12	V13	V14	V16	
	FWT (g)	3.55	3.26	3.69	3.64	3.53	3.80	3.58	3.60	3.47	3.58	3.39	3.43	3.68	3.77	3.70	3.36	
3	Sex	H	F	H	F	H	F	H	F	H	F	H	H	F	F	H		
	Findings																	
	Implant Type*	17	18	19	20													
	FWT (g)		17	18	19	V20												
	Sex		3.79	3.26	3.73	3.35												
	Findings																	

M = male  
 ED = early death

F = female  
 FWT = foetal weight

C = cervix  
 \* = viable foetuses are identified by assigned foetal number

APPENDIX VI  
 (contd)  
 IPPD : ORAL GAVAGE TERATOLOGY STUDY IN THE RAT  
 INDIVIDUAL CAESARIAN AND MACROSCOPIC FOETUS  
 NECROPSY FINDINGS

GROUP: 1

DOSE LEVEL (mg/kg): 0											
Dose Number	Parameter	Implantation Number									
		Left Horn of Uterus						Right Horn of Uterus			
		1	2	3	4	5	6	7	8	9	10
4	Implant Type*	V1	V2	V3	V4	V5	V6	V7	V8	C	V9
	FWT (g)	3.43	3.33	3.72	3.67	3.75	3.71	3.23	3.90	3.67	3.74
4	Sex	F	F	H	F	H	H	H	F	H	H
	Findings										
4	Implant Type*	V17	V18	V19							
	FWT (g)	3.44	3.41	2.78							
(contd)	Sex	H	H	H							
	Findings										
5	Implant Type*	V1	V2	V3	V4	V5	V6	V7	V8	C	V9
	FWT (g)	3.86	3.62	3.44	3.68	3.45	3.86	3.44	3.83	3.54	3.91
5	Sex	H	H	F	H	F	H	F	H	H	H
	Findings										
6	Implant Type*	V1	V2	V3	V4	V5	V6	ED	C	V7	V8
	FWT (g)	3.86	3.48	3.78	3.78	3.31	4.14			3.67	3.61
6	Sex	F	H	H	H	F	H			F	V9
	Findings										
7	Implant Type*	V1	V2	V3	V4	V5	V6	V7	C	V8	V9
	FWT (g)	3.74	3.70	4.32	4.17	4.22	4.53	4.16	3.85	3.92	3.80
7	Sex	F	F	H	H	H	H	F	F	F	V10
	Findings										

M = male  
 ED = early death

F = female  
 FWT = foetal weight

C = cervix  
 \* = viable foetuses are identified by assigned foetal number

A P P E N D I X  
(contd)

VII INDIVIDUAL CAESARIAN AND MACROSCOPIC FOETUS  
NECROPSY FINDINGS

GROUP: 1

DOSE LEVEL (mg/kg): 0

Dose Number	Parameter	Implantation Number																
		Left Horn of Uterus			Right Horn of Uterus													
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	
8	Implant Type*	C	V1	V2	V3	V4	V5	V6	V7	V8								
	FWT (g)	3.13	3.55	3.51	3.48	3.70	3.85	3.50	3.26									
	Sex	F	H	H	F	H	H	F	F									
	Findings																	
9	Implant Type*	V1	V2	V3	ED	V4	V5	V6	V7	C	V8	V9	V10	V11	V12	V13	V14	
	FWT (g)	3.41	3.91	3.44		3.75	3.88	3.98			3.83	3.92	3.48	3.89	3.84	3.85	3.49	3.64
	Sex	H	H	F		F	H	H		H	H	F	H	H	F	H		
	Findings																	
10	Implant Type*	V1	V2	V3	V4	V5	V6	V7	C	V8	V9	V10	V11	V12	V13	V14	V16	
	FWT (g)	3.79	3.87	4.61	4.27	3.52	4.13	4.18	4.34	4.05	3.85	3.94	4.27	3.86	3.86	3.85	3.97	
	Sex	F	F	H	H	F	H	F	H	F	H	H	H	F	F	H		
	Findings																	
11	Implant Type*	V1	V2	V3	V4	C	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	
	FWT (g)	3.58	3.74	3.83	3.89	3.94	4.04	4.04	3.92									
	Sex	F	F	H	H	F	H	H	F	H	H							
	Findings																	

M = male  
ED = early death

F = female  
FWT = foetal weight

C = cervix

\* = viable foetuses are identified by assigned foetal number

APPENDIX VI INDIVIDUAL CAESARIAN AND MACROSCOPIC FOETUS  
(contd)

GROUP: 1 DOSE LEVEL (mg/kg): 0

Dam Number	Parameter	Implantation Number																
		Left Horn of Uterus					Right Horn of Uterus											
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	
	Implant Type*	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	C	V11	ED	V12	V13	V14	V15
	FWT (g)	3.21	2.63	2.85	3.56	3.38	3.34	3.72	3.63	3.35	3.57	3.48		3.38	3.32	3.30	3.44	
12	Sex	H	H	F	H	F	F	H	H	H	F		H	F	F	F	H	
	Findings																	
	Implant Type*	17	18	19														
	FWT (g)	3.10	3.15	3.30														
12	Sex	F	F	F														
	Findings																	
	Implant Type*	V1	V2	V3	V4	C	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16
	FWT (g)	3.99	3.67	3.62	3.43	3.68	3.67	3.39	3.57	3.84	3.38	4.09	3.55	3.80	3.38	3.22	3.54	
13	Sex	H	H	F	F	H	H	F	H	H	F	H	F	H	F	F	H	
	Findings																	
	Implant Type*	17	17															
	FWT (g)	3.60	3.60															
13	Sex	H	H															
	Findings																	
	Implant Type*	V1	V2	V3	V4	V5	V6	V7	V8	V9	C	V10	V11	V12	V13	V14	V15	
	FWT (g)	3.92	4.16	4.33	4.47	2.82	4.63	3.99	4.40	4.27	4.09		4.24	4.33	4.79	4.67	4.68	
14	Sex	F	H	H	H	F	H	F	F	F	F		F	F	F	F	H	
	Findings																	

M = male

F = female

ED = early death

C = cervix

\* = viable foetuses are identified by assigned foetal number

**APPENDIX VI**  
**(contd)**  
**INDIVIDUAL CAESARIAN AND MACROSCOPIC FOETUS**  
**NECROPSY FINDINGS**

**GROUP: 1**

Dose Number	Parameter	Implantation Number																
		Left Horn of Uterus				Right Horn of Uterus												
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16			
15	Implant Type*	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	C	V12	V13	V14	V15	V16
	FWT (g)	3.65	3.86	3.86	3.51	3.76	3.89	3.55	4.18	3.89	4.39	4.07	4.01	3.79	3.68	3.08	3.43	
	Sex	F	F	H	H	F	F	F	H	F	H	H	H	H	H	F		
	Findings																	
15	Implant Type*	V17	V18	V19														
	FWT (g)	3.57	3.69	3.35														
	Sex	F	F	F														
	Findings																	
16	Implant Type*	V1	V2	V3	V4	V5	V6	V7	V8	C	V9	V10	V11	V12	V13	V14	V15	V16
	FWT (g)	4.08	4.10	4.03	3.90	3.68	4.13	3.99	4.09	4.00	3.51	3.82	3.64	4.07	3.48	4.06	3.42	
	Sex	H	H	F	H	F	H	F	H	F	H	F	F	F	H	F	H	
	Findings																	
17	Implant Type*	V1	V2	V3	V4	V5	V6	C	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16
	FWT (g)	3.57	3.32	3.48	3.63	3.63	3.75	3.81	3.77	3.99	3.63	3.72	3.39	3.91	3.63	3.72	3.88	
	Sex	H	F	H	F	F	F	H	F	H	F	F	F	H	F	F	H	
	Findings																	

M = male  
 ED = early death

F = female  
 FWT = foetal weight

C = cervix  
 \* = viable foetuses are identified by assigned foetal number

**APPENDIX VI**  
**INDIVIDUAL CAESARIAN AND MACROSCOPIC FOETUS**  
**(contd)**  
**NECROPSY FINDINGS**

**GROUP: 1**

**DOSE LEVEL (mg/kg): 0**

Dam Number	Parameter	Implantation Number																
		Left Horn of Uterus				Right Horn of Uterus												
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16			
	Implant Type*	V1	V2	V3	ED	V4	V5	V6	V7	V8	V9	C	V10	V11	V12	V13	V14	V15
	FWT (g)	3.64	2.79	3.64		3.63	3.59	3.44	3.58	3.30	3.16		3.58	3.35	3.61	3.41	3.48	3.24
18	Sex	H	F	H		F	F	F	F	F	H		F	H	F	F	F	F
	Findings																	
	Implant Type*																	
	FWT (g)																	
18	(contd)																	
	Findings																	
	Implant Type*																	
	FWT (g)																	
19	Sex	H	F	H		H	H	H	H	H	F		F	H	F	H	V10	V11
	Findings																	
	Implant Type*																	
	FWT (g)																	
20	Sex	H	F	H	H	H	H	H	H	H	H		F	H	F	H		
	Findings																	
	Implant Type*																	
	FWT (g)																	
21	Sex	F	F	H	H	H	F	F	F	F	F		F	H	F	F	F	F
	Findings																	

H = male

ED = early death

F = female

FWT = foetal weight

C = cervix

\* = viable foetuses are identified by assigned foetal number

APPENDIX VI  
(contd)IPPD : ORAL GAVAGE TERATOLOGY STUDY IN THE RAT  
INDIVIDUAL CAESARIAN AND MACROSCOPIC FOETUS  
NECROPSY FINDINGS

GROUP: 1

		DOSE LEVEL (mg/kg): 0															
Dam Number	Parameter	Left Horn of Uterus						Implantation Number						Right Horn of Uterus			
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
	Implant Type*	V1	V2	V3	V4	V5	V6	V7	V8	V9	C	V10	V11	V12	V13	V14	V15
	FWT (g)	3.51	4.51	4.12	3.72	3.75	4.16	4.31	4.22	4.08	4.03	4.12	4.04	4.22	4.14	4.42	3.80
22	Sex	F	H	H	F	F	H	H	H	H	F	F	F	F	H	H	F
	Findings																
	Implant Type*	V17	V18	V19													V16
	FWT (g)	3.94	4.01	3.96													
22	Sex	F	F	F													
	Findings																
	Implant Type*	V1	V2	V3	V4	V5	V6	V7	C	V8	V9	V10	V11	V12	E0	V13	
	FWT (g)	4.17	4.00	4.03	4.03	4.05	ED	4.32	4.00	4.24	4.01	4.21	4.25	3.91	4.23		
(contd)	Sex	F	F	F	F	H	H	H	H	F	H	F	H	F	H		
	Findings																
	Implant Type*	V1	V2	ED	V3	V4	V5	V6	V7	V8	C	V10	V11	V12	V13	V14	V15
	FWT (g)	3.18	3.01		3.11	3.32	3.47	3.02	3.11	3.31	3.43	3.35	3.54	3.27	3.47	2.82	3.18
23	Sex	H	F		F	H	F	H	F	H	F	H	F	H	F	H	
	Findings																
	Implant Type*	V16	V17	V18	ED												
	FWT (g)	3.20	2.93	3.38													
(contd)	Sex	H	F	H													
	Findings																

H = male  
ED = early death

F = female

FWT = foetal weight

C = cervix

\* Viable foetuses are identified by assigned foetal number

A P P E N D I X      V I  
 (contd)

IPPD : ORAL GAVAGE TERATOLOGY STUDY IN THE RAT  
 INDIVIDUAL CAESARIAN AND MACROSCOPIC FOETUS  
 NECROPSY FINDINGS

GROUP: 2

DOSE LEVEL (mg/kg): 12.5

Dam Number	Parameter	Implantation Number																
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	
	Implant Type*	V1	V2	V3	V4	V5	V6	V7	C	V8	V9	V10						
	FWT (g)	5.36	4.06	5.13	5.40	5.35	5.06	5.50	5.64	5.91	4.82							
25	Sex	H	F	H	F	H	F	H	F	H	F							
	Findings																	
	Implant Type*	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	C	V12	V13	V14	V15	
	FWT (g)	4.17	4.22	3.93	3.99	4.18	4.43	4.61	3.89	4.24	4.11	4.16	4.18	4.10	4.23	4.24		
26	Sex	H	H	H	F	H	H	H	F	F	F	F	H	H	F	F		
	Findings																	
	Implant Type*	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	C	V12	V13	V14	V15	
	FWT (g)	4.37	4.37	V16	V17													
26	Sex			F	F													
(contd)	Findings																	
	Implant Type*	V1	V2	V3	V4	V5	V6	V7	V8	V9	C	V10	V11	V12	V13	ED		
	FWT (g)	3.25	3.60	4.14	3.59	3.41	3.44	3.71	3.82	3.88	3.92	4.09	4.32	3.61				
27	Sex	H	H	H	F	H	H	H	F	F	F	H	F	H	F	F		
	Findings																	
	Implant Type*	V1	V2	V3	V4	V5	V6	V7	C	V8	V9	V10	V11	V12	V13	V14	V15	V16
	FWT (g)	5.47	5.39	6.02	6.12	6.19	5.81	6.04	5.60	6.24	5.41	5.55	5.41	6.00	6.22	5.36	5.53	
28	Sex	F	F	H	H	H	H	H	F	H	H	F	H	F	H	F		
	Findings																	

H = male  
 ED = early death

F = female  
 FWT = foetal weight

C = cervix  
 \* = viable foetuses are identified by assigned foetal number

**APPENDIX VI**  
**(contd)**

**IPPD : ORAL GAVAGE TERATOLOGY STUDY IN THE RAT  
 INDIVIDUAL CAESARIAN AND MACROSCOPIC FOETUS  
 NECROPSY FINDINGS**

**GROUP: 2**

**DOSE LEVEL (mg/kg): 12.5.**

Dam Number	Parameter	Implantation Number																
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	
29	Implant Type*	V1	V2	V3	C	V4	ED	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15
	FWT (g)	3.93	3.71	3.98	3.88	3.90		3.78	3.72	3.58	3.35							
	Sex	H	F	H	F	H		H	H	F	F							
	Findings																	
30	Implant Type*	V1	V2	V3	V4	ED	V5	V6	V7	C	V8	V9	V10	V11	V12	V13	V14	V15
	FWT (g)	3.86	3.96	4.19	4.13		4.20	3.94	3.84	4.10	4.69							
	Sex	H	F	F	F		H	F	F	H	H							
	Findings																	
31	Implant Type*	V1	V2	V3	ED	V4	V5	V6	V7	V8	C	V9	V10	V11	V12	V13	V14	V15
	FWT (g)	3.25	3.13	3.51		3.61	3.82	3.55	3.35	3.61	3.69	3.63	3.13	3.92	3.29	3.45	3.39	3.39
	Sex	H	H	F		H	F	F	F	H	H							
	Findings																	
31 (contd)	Implant Type*	V16	V17															
	FWT (g)	3.62	2.86															
	Sex	H	F															
	Findings																	
32	Implant Type*	V1	V2	V3	V4	V5	V6	V7	V8	V9	C	V10	V11	V12	V13	V14	V15	
	FWT (g)	3.64	4.04	3.54	3.49	3.83	3.36	3.55	3.53	3.75	3.52	3.64	3.44	3.56	3.65	3.44		
	Sex	H	H	H	F	H	F	N	H	F	N	F	H	N	N	F		
	Findings																	

H = male

F = female

ED = early death

C = cervix

\* = viable foetuses are identified by assigned foetal number

**APPENDIX V I**  
**INDIVIDUAL CAESARIAN AND MACROSCOPIC FOETUS**  
**NECROPSY FINDINGS**

**GROUP: 2**

		Parameter	Implantation Number										Right Horn of Uterus					
Dam Number			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
33	Implant Type*	V1	V2	V3	V4	V5	V6	V7	V8	C	ED	V9	V10	V11	V12	V13	V14	V15
	FWT (g)	3.46	3.93	3.55	4.19	3.49	3.48	3.69	3.91			3.58	3.81	3.72	3.60	3.67	3.16	3.46
	Sex	N	N	F	N	F	F	F	N			F	F	N	N	F	N	
	Findings																	
34	Implant Type*	V1	V16	V17														
	FWT (g)	3.33	3.25															
	Sex	N	N	F														
	Findings																	
35	Implant Type*	V1	ED	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13			
	FWT (g)	3.42	3.62	3.89	3.75	ED	ED	V5	V6	C	V7	V8	V9	V10	V11	V12	V13	
	Sex	F	F	N	F	F	F	N	F		F	N	F	F	N	F	F	
	Findings	e,f																
35	Implant Type*	17	18															
	FWT (g)	ED	V14															
	Sex		3.79															
	Findings		H															

M = male  
 ED = early death

F = female  
 FWT = foetal weight

C = cervix  
 \* = viable foetuses are identified by assigned foetal number

A P P E N D I X      VI      INDIVIDUAL CAESARIAN AND MACROSCOPIC FOETUS  
 (contd)

GROUP: 2

DOSE LEVEL (mg/kg): 12.5

Den Number	Parameter	Implantation Number															
		Left Horn of Uterus					Right Horn of Uterus										
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
	Implant Type*	V1	V2	V3	V4	V5	V6	V7	C	V8	V9	V10	V11	V12	V13	V14	V15
	FWT (g)	3.76	3.71	3.86	3.97	3.67	3.64	3.73	3.92	3.57	3.73	3.76	3.58	3.47	3.67	3.74	
36	Sex	H	F	H	H	H	H	F	F	H	H	H	F	F	F	H	
	Findings																
	Implant Type*	V1	V2	V3	V4	V5	C	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15
	FWT (g)	3.83	3.94	4.19	3.89	4.06	2.28	3.78	4.02	4.06	4.30	4.15	4.02	3.51	4.04	3.64	4.24
37	Sex	F	H	H	F	F	H	F	F	H	F	H	F	F	H	F	H
	Findings																
	Implant Type*	V17															
	FWT (g)	3.62															
37	Sex																
(contd)	Findings																
	Implant Type*	V1	V2	V3	V4	C	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15
	FWT (g)	4.03	3.99	4.75	4.47	4.60	4.36	4.50	4.34	4.53	4.22	4.21	4.47	4.42	4.24	4.12	3.66
38	Sex	H	F	H	H	H	H	F	H	H	F	H	H	H	H	F	F
	Findings																
	Implant Type*	V1	V2	V3	V4	V5	V6	V7	C	V8	ED	V9	V10	V11	V12	V13	V14
	FWT (g)	3.96	3.63	3.71	3.73	3.71	4.05	3.71	3.36	3.61	3.93	3.61	3.81	3.48	3.67	3.61	3.51
39	Sex	H	F	H	F	-	F	F	F	H	H	H	F	H	H	F	
	Findings																

H = male

ED = early death

F = female

FWT = foetal weight

C = cervix

\* = viable foetuses are identified by assigned foetal number

A P P E N D I X V I  
 (contd)  
 INDIVIDUAL CAESARIAN AND MACROSCOPIC FOETUS  
 NECROPSY FINDINGS

GROUP: 2

DOSE LEVEL (mg/kg) : 12.5

Dam Number	Parameter	Implantation Number															
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
39 (contd)	Implant Type <sup>*</sup> FWT (g)	17 V16 3.33															
	Sex	F															
	Findings																
40 (contd)	Implant Type <sup>*</sup> FWT (g)	17 V1 4.09 3.98	V2 F	V3 H	V4 F	V5 H	V6 H	V7 F	V8 N	V9 F	V10 N	V11 F	V12 F	V13 F	V14 F	V15 N	V16 N
	Sex	F															
	Findings																
41 (contd)	Implant Type <sup>*</sup> FWT (g)	17 V17 3.69 3.72	V2 F	V3 H	V4 F	V5 N	V6 F	V7 N	V8 F	V9 N	V10 F	V11 N	V12 N	V13 N	V14 N	V15 N	V16 N
	Sex	F															
	Findings																
41 (contd)	Implant Type <sup>*</sup> FWT (g)	17 V17 3.73 4.02	V18 F	V18 H													
	Sex	F															
	Findings																

M = male  
 ED = early death

F = female  
 FWT = foetal weight

C = cervix  
 \* = viable foetuses are identified by assigned foetal number

A F P E N D I X V I  
 (contd)

IPPD : ORAL GAVAGE TERATOLOGY STUDY IN THE RAT  
 INDIVIDUAL CAESARIAN AND MACROSCOPIC FOETUS  
 NECROPSY FINDINGS

GROUP: 2

DOSE LEVEL (mg/kg): 12.5

Dose Number	Parameter	Implantation Number										Right Horn of Uterus					
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	
	Implant Type*	V1	V2	V3	V4	V5	V6	V7	V8	V9	C V10	V11	V12	V13	V14	V15	
	FUT (g)	3.58	3.39	3.74	3.43	3.66	2.82	3.85	3.67	3.61	3.82	3.69	3.70	4.04	4.20	3.56	3.82
42	Sex	M	M	M	F	F	M	F	F	M	M	H	H	F	H	F	
	Findings																
	Implant Type*	V17	V18	V19													V16
	FUT (g)	3.65	3.39	3.08													
42	Sex	M	M	M	F												
	Findings																
	Implant Type*	V1	V2	ED	V3	V4	V5	V6	V7	V8	C V9	ED	V10	V11	ED		
	FUT (g)	3.21	4.00		1.52	3.76	4.04	3.38	2.90	3.90	3.36		3.45	3.79			
43	Sex	F	M	M	M	M	F	F	F	F	F		F	M			
	Findings																
	Implant Type*	V1	V2	V3	V4	V5	V6	V7	V8	C V9	V10	V11	V12	V13	V14	V15	V16
	FUT (g)	3.77	3.93	3.69	3.58	3.85	3.81	4.05	4.48	3.29	3.88	4.13	3.41	4.15	3.97	4.00	4.19
44	Sex	M	M	F	F	F	M	M	F	F	M	F	H	H	F	H	
	Findings																
	Implant Type*	V17	V18	V19	V20												
	FUT (g)	3.52	4.00	3.39	3.50												
44	Sex	F	M	M	H												
	Findings																

M = male  
 ED = early death

F = female  
 FWT = foetal weight

C = cervix  
 \* = viable foetuses are identified by assigned foetal number

**A P P E N D I X      VI      INDIVIDUAL CAESARIAN AND MACROSCOPIC FOETUS  
(contd)**

**GROUP: 2**

**DOSE LEVEL (mg/kg): 12.5**

Dam Number	Parameter	Implantation Number																
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	
45	Implant Type*	V1	V2	V3	V4	V5	V6	V7	V8	C	ED	ED	V9	V10	V11	V12	V13	V14
	FWT (g)	3.65	3.84	3.75	3.84	3.52	3.94	3.62	4.21				3.94	3.83	3.79	3.89	3.49	3.55
	Sex	F	H	H	F	F	H	F	H				H	F	F	H	F	F
	Findings																	
45	Implant Type*	V15	17															
	FWT (g)	3.32																
	Sex	F																
	Findings																	
46	Implant Type*	V1	V2	V3	V4	V5	V6	V7	V8	C	V9	V10	V11	V12	V13	V14	V15	V16
	FWT (g)	3.73	3.62	3.66	3.81	3.97	3.79	3.96	3.96	3.90	3.72	3.76	3.88	3.71	3.53	3.55	3.55	3.63
	Sex	H	F	F	H	H	F	F	H	H	H	H	F	H	F	F	F	
	Findings																	
47	Implant Type*	V1	V2	V3	V4	V5	V6	C	ED	V7	V8	V9	V10	V11	V12	V13	V14	V15
	FWT (g)	3.40	3.15	3.41	3.73	3.47	3.67			3.21	3.52	3.51	3.22	3.21	3.65	3.37	3.06	3.06
	Sex	F	F	H	H	F	F			F	H	F	F	F	H	F	F	
	Findings																	
48	Implant Type*	V1	V2	V3	V4	V5	V6	V7	ED	V8	V9	V10 C	V11	V12	V13	ED	V14	
	FWT (g)	3.82	3.78	3.94	3.85	3.78	3.69	3.32		3.75	4.02	3.97	3.91	4.10	3.60		3.95	
	Sex	H	F	H	H	H	F	F		H	H	F	F	H	F			
	Findings																	

H = male  
ED = early death

F = female  
FWT = foetal weight

C = cervix  
\* = Viable foetuses are identified by assigned foetal number

APPENDIX VI INDIVIDUAL CAESARIAN AND MACROSCOPIC FOETUS  
NECROPSY FINDINGS  
(contd)

GROUP: 2

DOSE LEVEL (mg/kg): 12.5

Dam Number	Parameter	Implantation Number														
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
48 (contd)	Implant Type*	17	18													
	FWT (g)	15	16													
	Sex	3.29	3.67													
	Findings															

M = male

F = female

FWT = foetal weight

C = cervix  
\* Viable foetuses are identified by assigned foetal number

APPENDIX VI  
(contd)

GROUP: 3

Dam Number	Parameter	Implantation Number																			
		Left Horn of Uterus				Right Horn of Uterus															
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16				
	Implant Type*	V1	ED	V2	V3	C	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15			
	FET (g)	3.52	4.03	3.86	3.60	3.71	3.69	3.95	3.84	4.19	3.93	3.76	3.92	3.95	3.90	3.90	3.56				
49	Sex	F	F	H	F	H	H	F	H	F	H	F	H	H	H	H	H				
	Findings																g				
	Implant Type*	V1	ED	ED	V2	ED	V3	C	V4	V5	V6	V7	C	V8	V9	V10	V11	V12	V13	V14	V15
	FET (g)	2.92	F			2.73				3.69	4.40	4.11									
50	Sex									H	H	F									
	Findings	a,c,h																			
	Implant Type*	V1	V2	V3	V4	ED	V5	V6	V7	V8	C	V9	V10	V11	V12	V13	V14	V15	V16		
	FET (g)	5.29	5.21	5.07	5.24		5.12	5.46	5.34	5.61	5.24	5.14	5.58	5.25	5.62	5.17	5.19				
51	Sex	H	H	H	H		F	F	F	H	F	F	H	F	H	j	H	H	H		
	Findings																				
	Implant Type*	V1	V2	V3	V4	V5	V6	V7	V8	C	V9	V10	V11	V12	V13	V14	V15	V16			
	FET (g)	3.96	4.08	3.81	4.35	4.38	4.15	4.25	4.18	4.26	3.81	3.98	4.38	4.02	4.42	4.33	4.05				
52	Sex	F	N	F	H	H	H	F	F	H	F	H	H	F	H	H	H	H	F		
	Findings	a																			
	Implant Type*	V1	ED	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16			
	FET (g)	2.29	3.35	3.19	3.55	3.63	3.37	3.27	3.21	3.45	3.42	3.57	3.45	3.57	3.48	3.48	3.36				
53	Sex	H	F	F	H	H	F	F	H	F	H	F	H	H	H	H	H	H	F		
	Findings	a																			

H = male  
ED = early death

F = female  
FWT = foetal weight

C = cervix  
\* = viable foetuses are identified by assigned foetal number

A P P E N D I X  
(contd)

GROUP: 3

IPPD : ORAL GAVAGE TERATOLOGY STUDY IN THE RAT  
VI INDIVIDUAL CAESARIAN AND MACROSCOPIC FOETUS  
NECROPSY FINDINGS

Data Number	Parameter	Implantation Number																
		Left Horn of Uterus				Right Horn of Uterus												
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	
54	Implant Type*	V1	V2	V3	V4	V5	V6	V7	V8	V9	C	V10	V11	V12	V13	V14	V15	V16
	FWT (g)	3.72	3.81	3.52	3.09	3.49	3.81	4.03	3.69	3.90	3.68	3.83	3.52	3.82	3.81	3.71	3.66	
	Sex	H	H	F	H	H	H	H	F	H	H	F	H	F	H	F	F	
	Findings																	
54	Implant Type*	17	V17															
	FWT (g)		3.72															
	Sex			H														
	Findings																	
55	Implant Type*	V1	V2	V3	V4	V5	V6	V7	V8	V9		V10	V11 C	V12	V13	V14	V15	V16
	FWT (g)	3.15	2.87	3.60	3.45	3.58	3.55	3.58	3.60	3.63		3.31	3.44	3.80	3.52	3.68	3.77	3.78
	Sex	F	F	F	H	H	H	F	H	F		F	H	H	H	H	F	
	Findings																	
55	Implant Type*	17	18	19	20	21												
	FWT (g)	3.72	3.18	3.49	3.31	3.78												
	Sex	H	F	H	F	H												
	Findings																	
56	Implant Type*	V1	V2	V3	V4	V5	C	V6	V7	V8	V9	ED	V10	V11	V12			
	FWT (g)	3.43	3.94	4.08	3.99	4.13	4.07	3.22	3.62	4.00								
	Sex	F	H	F	H	H	-	H	F	H								
	Findings																	

H = male  
ED = early death

F = female  
FWT = foetal weight

C = cervix  
\* = viable foetuses are identified by assigned foetal number

**APPENDIX VI** IPPD : ORAL GAVAGE TERATOLOGY STUDY IN THE RAT  
 (contd)

**GROUP: 3**

Dam Number	Parameter	Implantation Number														DOSE LEVEL (mg/kg): 62.5	
		Left Horn of Uterus		Right Horn of Uterus													
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16		
57	Implant Type*	V1	V2	V3	V4	V5	V6	V7	C	ED	ED						
	FWT (g)	3.17	3.06	4.08	4.49	2.68	4.18	4.10									
	Sex	F	F	H	H	F	F										
	Findings																
58	Implant Type*	V1	V2	V3	ED	V4	V5	V6	V7	C	V9	V10	V11	V12	V13	V14	V15
	FWT (g)	3.28	3.45	3.26		3.43	3.53	3.88	3.78	3.82	2.74	3.19	3.41	3.67	3.21	3.86	3.62
	Sex	H	F	F		F	F	H	H	H		F	H	F	H	H	
	Findings																
59	Implant Type*	V1	V2	V3	V4	C	V5	V6	ED	V7	V8	V9	V10	V11	V12	V13	V14
	FWT (g)	3.16	3.33	3.75	3.64	3.57	2.81			3.52	3.54	3.80	3.71	3.38	3.46	3.09	
	Sex	F	F	H	H	F	F		H	F	H	H	H	F	F		
	Findings																
60	Implant Type*	V1	V2	V3	ED	V4	V5	V6	V7	C	V8	V9	V10	V11	V12	V13	V14
	FWT (g)	4.00	4.06	4.43		3.96	4.00	4.27	3.87	3.97	3.41	3.93	4.35	4.35	4.38	3.80	
	Sex	F	F	H		F	H	H	F	F	F	F	F	H	H	F	
	Findings																
61	Implant Type*	V1	V2	V3	V4	V5	C	V6	V7	V8	V9	V10	V11	V12	V13	ED	V14
	FWT (g)	4.34	4.57	4.28	4.10	3.69	3.88	4.09	3.98	4.08	3.82	4.09	4.02	3.77			4.30
	Sex	H	H	F	F	F	F	H	H	F	F	F	F	H		H	
	Findings																

H = male  
 ED = early death

F = female  
 FWT = foetal weight

C = cervix  
 \* = viable foetuses are identified by assigned foetal number

A P P E N D I X  
 (contd)

V I      IPPD : ORAL GAVAGE TERATOLOGY STUDY IN THE RAT  
 INDIVIDUAL CAESARIAN AND MACROSCOPIC FOETUS  
 NECROPSY FINDINGS

GROUP: 3

DOSE LEVEL (mg/kg): 62.5

Dose Number	Parameter	Implantation Number															
		Left Horn of Uterus						Right Horn of Uterus									
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
	Implant Type*	V1	V2	V3	V4	V5	V6	ED	V7	C	V8	V9	V10	V11	V12	V13	V14
62	FWT (g)	4.22	4.42	4.10	4.07	4.03	3.70		2.81	4.02	3.81	3.72	3.84	4.02	3.91	3.86	
	Sex	M	M	F	F	N	F		N	F	F	N	N	N	F	F	
	Findings																
	Implant Type*	V1	V2	V3	V4	V5	V6	C	V7	V8	V9	V10	V11	V12	V13	V14	V15
63	FWT (g)	3.34	3.51	3.08	3.69	3.76	3.74	3.59	3.35	3.62	3.77	4.09	3.75	3.48	3.53	3.83	3.64
	Sex	F	F	F	N	N	F	F	F	N	N	N	N	F	N	N	N
	Findings																
	Implant Type*	CV1	V2	V3													
64	FWT (g)	3.99	3.21	3.99													
	Sex	F	F	F													
	Findings																
	Implant Type*	V1	V2	V3	V4	V5	V6	V7	ED	C	ED	V8	V9	V10	V11	V12	V13
65	FWT (g)	3.86	3.46	3.74	3.61	3.65	3.76	4.20				4.18	3.62	3.89	3.83	3.44	3.53
	Sex	M	F	F	N	F	F	F				N	N	N	F	F	F
	Findings																
	Implant Type*	17															
65	FWT (g)		V15														
(contd)	Sex		3.50														
	Findings		F														

M = male  
 ED = early death

F = female  
 FWT = foetal weight

C = cervix  
 \* = viable foetuses are identified by assigned foetal number

**A P P E N D I X V I**  
**(contd)**  
**IPPD : ORAL GAVAGE TERATOLOGY STUDY IN THE RAT**  
**INDIVIDUAL CAESARIAN AND MACROSCOPIC FOETUS**  
**NECROPSY FINDINGS**

**GROUP: 3**

**DOSE LEVEL (mg/kg): 62.5**

Item Number	Parameter	Implantation Number										Right Horn of Uterus				
		Left Horn of Uterus					V1    V2    V3    V4    V5    V6    V7    V8    V9    V10    V11    V12    V13    V14    V15    V16					1    2    3    4    5    6    7    8    9    10    11    12    13    14    15    16				
66	Implant Type*	V1	V2	V3	V4	V5	V6	V7	V8	V9	C	V10	V11	V12	V13	V14
	FET (g)	4.43	3.28	4.37	4.28	4.16	4.32	4.02	4.13	4.43	4.41	4.11	4.24	3.90	4.61	4.57
	Sex	H	F	F	F	H	F	H	F	F	F	F	F	F	H	F
	Findings															
66	Implant Type*	V17	V18													
	FET (g)	4.06	4.01													
	Sex	F	F													
	Findings															
67	Implant Type*	V1	V2	ED	V3	V4	ED	V5	C	V6	ED	V7	V8	V9	V10	V11
	FET (g)	3.52	2.34		2.93	3.13		2.67	2.66			2.35	3.28	3.04	2.89	2.17
	Sex	H	F		F	F		F	F			F	H	F	F	
	Findings															
68	Implant Type*	V1	V2	V3	V4	V5	V6	V7	V8	V9	C	ED	V10	V11	V12	V13
	FET (g)	3.73	4.17	4.26	4.46	4.06	4.08	4.10	4.22	4.25	4.25	4.00	3.90	4.12	4.28	V14
	Sex	F	F	H	H	H	F	H	H	H	H	F	F	F	H	
	Findings															
69	Implant Type*	V1	ED	V2	V3	V4	V5	V6	V7	C	V8	V9	V10	V11	V12	V13
	FET (g)	3.95		3.99	3.65	3.56	3.64	3.69	4.14	3.66	3.64	3.60	3.61	3.71	3.68	3.80
	Sex	H		H	F	F	H	F	H	F	F	F	H	F	F	
	Findings															

H = male  
ED = early death

F = female  
FWT = foetal weight

C = cervix  
\* = viable foetuses are identified by assigned foetal number

**A P P E N D I X V I**  
(contd)

**IPPD : ORAL GAVAGE TERATOLOGY STUDY IN THE RAT  
INDIVIDUAL CAESARIAN AND MACROSCOPIC FOETUS  
NECROPSY FINDINGS**

**GROUP: 3**

**DOSE LEVEL (mg/kg): 62.5**

Dose Number	Parameter	Implantation Number														
		Left Horn of Uterus				Right Horn of Uterus										
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	
Implant Type*	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10 c	V11	V12	V13	V14	V15	V16
FNT (g)	3.95	4.12	4.27	3.94	3.96	3.79	4.27	3.49	3.14	3.86	3.99	4.02	3.97	3.78	4.04	3.94
70 Sex	F	H	H	H	F	F	H	H	F	F	F	F	F	F	F	F
Findings																
Implant Type*	V17	V18														
FNT (g)	3.81	3.62														
70 (contd) Sex	H	H														
Findings																
Implant Type*	V1	V2	V3	V4	V5	V6	V7 c	V8	V9	V10	V11	V12	V13	V14	V15	
FNT (g)	3.41	3.62	3.74	3.82	3.81	4.01	3.73	3.43	3.44	3.65	3.48	3.64	4.12	3.79	3.61	
71 Sex	F	F	H	H	H	F	F	F	F	F	F	F	H	H	H	
(contd) Findings																
Implant Type*	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12 c	V13	V14	V15	
FNT (g)	3.48	4.04	4.08	3.67	3.85	3.79	3.88	4.33	4.07	3.66	3.57	4.40	4.23	3.92	4.39	
72 Sex	H	H	H	F	F	H	H	H	F	F	H	H	H	H		
Findings																

H = male  
ED = early death

F = female  
FNT = foetal weight

C = cervix  
\* = viable foetuses are identified by assigned foetal number

**A P P E N D I X V I      IPPD : ORAL GAVAGE TERATOLOGY STUDY IN THE RAT  
(contd)      INDIVIDUAL CAESARIAN AND MACROSCOPIC FOETUS  
NECROPSY FINDINGS**

**GROUP: 4**

**DOSE LEVEL (mg/kg): 125**

Dam Number	Parameter	Implantation Number																
		Left Horn of Uterus			Right Horn of Uterus													
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16			
Implant Type*		V1	V2	V3	V4	V5	V6	V7	C	V8	ED	V9	V10	V11	V12	V13	V14	V15
FWT (g)		3.60	3.70	3.66	3.82	3.91	3.58	3.94	4.23			3.47	3.63	3.57	4.22	3.97	2.79	3.68
73	Sex	M	M	F	M	F	F	F	M	F	M	F	N	F	N	F	F	F
Findings																		
Implant Type*		V17	V18	V19	V16	V17	V18	V17	V18	V19	V10	V11	V12	V13	V14	V15	V16	
FWT (g)		4.05	3.72	3.45														
73	(contd)																	
Findings																		
Implant Type*		V1	V2	V3	V4	V5	V6	V7	V8	V9	C	V10	V11	V12	V13	V14	V15	V16
FWT (g)		3.86	3.54	3.47	3.63	4.03	3.95	3.84	3.98	4.06	3.82	3.92	4.19	4.04	3.65	3.84	3.75	
74	Sex	M	F	F	F	M	F	N	F	N	F	F	M	F	F	F	F	
Findings																		
Implant Type*		V17	V18	V19	V20	V17	V18	V19	V20	V17	V18	V19	V20	V17	V18	V19	V16	
FWT (g)		4.00	3.61	3.42	3.40													
74	(contd)																	
Findings																		
Implant Type*		V1	V2	V3	V4	V5	V6	V7	C	V8	V9	ED	V10	V11	V12	V13	V14	V15
FWT (g)		4.27	4.36	3.98	3.88	4.38	4.21	3.79	4.19	4.48			3.61	4.41	4.35	4.37	3.98	4.14
76	Sex	M	M	F	M	F	F	F	F	F	F	F	F	F	H	H	F	H
Findings																		

M = male  
F = female  
ED = early death

F = foetal weight  
ED = foetal death

C = cervix  
\* = viable foetuses are identified by assigned foetal number

**A P P E N D I X      V I      INDIVIDUAL CAESARIAN AND MACROSCOPIC FOETUS  
(contd)                    NECROPSY FINDINGS**

**GROUP: 4                    DOSE LEVEL (mg/kg): 125**

Dam Number	Parameter	Implantation Number																
		Left Horn of Uterus			Right Horn of Uterus													
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	
	Implant Type*	17																
	FWT (g)	V16	3.37															
76 (contd)	Sex	F																
	Findings																	
	Implant Type*	V1	ED	V2	V3	V4	V5	V6	V7	V8	V9	C	V10	V11	V12	V13	V14	V15
	FWT (g)	3.18		3.13	3.24	3.52	3.75	3.55	3.41	3.50	3.64		3.48	3.33	3.90	3.60	3.43	3.26
77	Sex	H		F	H	H	H	H	F	F	F		F	F	N	F	F	F
	Findings																	
	Implant Type*	17																
	FWT (g)	V16	3.54															
77 (contd)	Sex	H																
	Findings																	
	Implant Type*	V1	V2	V3	V4	V5	V6	V7	C	V8	V9	V10	V11	V12	V13	V14	V15	
	FWT (g)	3.90	3.79	3.79	3.96	2.95	3.85	4.01	3.95	3.90	4.26	3.78	3.92	3.75	3.40			
78	Sex	H	F	F	H	F	F	F	F	F	F	F	F	F	F	F	F	
	Findings																	
	Implant Type*	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	C	V11	V12	V13	V14	V15	
	FWT (g)	3.55	4.20	4.25	3.97	3.83	4.07	4.24	4.14	4.02	4.50	4.40	4.22	4.85	3.82	4.07		
79	Sex	F	F	H	F	F	F	F	F	F	H	H	H	H	F	F	F	
	Findings																	

H = male  
ED = early death

F = female  
FWT = foetal weight

C = cervix  
\* = viable foetuses are identified by assigned foetal number

LD = late death

A P P E N D I X V I  
 (contd)  
 INDIVIDUAL CAESARIAN AND MACROSCOPIC FOETUS  
 NECROPSY FINDINGS

GROUP: 4 DOSE LEVEL (mg/kg): 125

Dose Number	Parameter	Implantation Number																
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	
79 (contd)	Implant Type*	17																
	FWT (g)	4.20																
	Sex	H																
	Findings																	
80 (contd)	Implant Type*	V1	V2	V3	V4	V5	V6	C	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16
	FWT (g)	3.85	3.58	3.60	3.77	3.41	3.90	3.71	3.68	3.95	4.20	3.87	3.97	3.72	4.02	3.83	3.84	
	Sex	F	F	F	F	F	F	F	F	N	N	F	F	F	N	N	F	
	Findings																	
80 (contd)	Implant Type*	17	18	19														
	FWT (g)	3.97	3.78	3.49														
	Sex	H	H	F														
	Findings																	
81 (contd)	Implant Type*	V1	V2	V3	V4	V5	V6	C	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16
	FWT (g)	3.82	3.88	4.20	4.36	3.91	4.07	4.16	4.40	4.08	4.05	4.40	4.25	4.00	3.60	3.60	3.65	3.99
	Sex	F	H	H	F	F	F	F	N	F	F	N	F	F	F	F	F	
	Findings																	
81 (contd)	Implant Type*	17	18															
	FWT (g)	3.93	4.28															
	Sex	F	H															
	Findings																	

M = male  
 F = female

FWT = foetal weight  
 V = viable foetuses are identified by assigned foetal number

C = cervix

APPENDIX VI  
(contd) INDIVIDUAL CAESARIAN AND MACROSCOPIC FOETUS  
NECROPSY FINDINGS

GROUP: 4

DOSE LEVEL (mg/kg): 125

Dam Number	Parameter	Implantation Number																
		Left Horn of Uterus						Right Horn of Uterus										
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	
	Implant Type*	V1	V2	V3	V4	V5	ED	V6	V7	V8	C	V9	ED	V10	V11	V12	V13	ED
	FET (g)	3.85	3.97	4.07	4.04	3.86		4.16	3.80	4.22	3.87			3.74	3.57	3.90	3.95	
82	Sex	F	H	H	F	H		H	H	H	H		H	F	F	F	H	
	Findings																	
	Implant Type*	17	V16															
	FET (g)		3.70															
82	Sex		F															
	(contd)																	
	Findings																	
	Implant Type*	V1	V2	V3	V4	V5	V6	V7	V8	C	V9	V10	V11	V12	V13	V14	ED	V15
	FET (g)	4.11	3.62	3.85	4.27	3.70	3.84	4.07	4.32	4.14	4.12	4.18	4.23	4.09	4.26			4.19
83	Sex	H	F	F	H	F	F	F	H	H	H	H	H	H	H	H	H	
	(contd)																	
	Findings																	
	Implant Type*	17	18	19														
	FET (g)	V16	V17	V18														
83	Sex	H	H	H	F	H		F	H	H	H	H	H	H	H	H	H	
	(contd)																	
	Findings																	
	Implant Type*	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	ED	
	FET (g)	4.26	4.41	3.93	4.06	3.67	4.14	4.09	4.25	3.39	4.73	4.46	4.33	4.64	4.31	3.91		
84	Sex	H	H	F	H	H	F	H	F	H	H	H	H	H	H	H	F	
	(contd)																	
	Findings																	

H = male  
ED = early death

F = female  
FET = foetal weight

C = cervix  
\* = viable foetuses are identified by assigned foetal number

**APPENDIX V I**  
**IPPD : ORAL GAVAGE TERATOLOGY STUDY IN THE RAT**  
**INDIVIDUAL CAESARIAN AND MACROSCOPIC FOETUS**  
**NECROPSY FINDINGS**

**GROUP: 4**

Dam Number	Parameter	Implantation Number														Right Horn of Uterus	DOSE LEVEL (mg/kg): 125	
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15		
	Implant Type*	V1	V2	V3	V4	V5	V6	V7	V8	C	V9	V10	V11	V12	V13	V14	V15	V16
	FWT (g)	4.22	4.17	4.11	4.41	4.35	3.89	4.42	4.16	4.23	4.08	4.53	3.98	4.13	4.10	3.81	4.12	
85	Sex	F	F	N	F	F	F	F	F	F	F	F	F	F	H	F	F	
	Findings																	
	Implant Type*	V17	V18															
	FWT (g)	4.03	3.66															
85 (contd)	Sex	F	F															
	Findings																	
	Implant Type*	V1	V2	V3	V4	V5	V6	V7	V8	C	V9	V10	V11	V12	V13	V14	V15	V16
	FWT (g)	3.60	3.52	3.51	3.81	3.80	3.80	3.74	3.63	4.05	3.68	3.94	3.79	3.66	3.93	3.55	3.43	
86	Sex	F	F	N	N	F	F	F	N	N	F	N	N	N	N	N	F	
	Findings																	
	Implant Type*	V1	V2	V3	V4	V5	V6	V7	V8	C	V9	V10	V11	V12	V13	V14	V15	V16
	FWT (g)	3.97	4.15	3.70	3.80	4.54	4.06	4.01	4.52	4.28	3.89	3.77	3.92	3.60	3.96	4.00		
87	Sex	F	H	F	F	H	F	H	N	N	F	F	F	F	H	H		
	Findings																	
	Implant Type*	V1	V2	V3	V4	V5	V6	V7	V8	C	V9	V10	V11	V12	V13	V14	V15	V16
	FWT (g)	3.37	3.72	3.40	3.64	3.99	3.96	4.11	3.86	3.61	3.39	3.93	3.72	3.81	3.69	3.77	3.42	
88	Sex	F	H	F	H	H	H	H	F	H	F	H	F	H	F	F	F	
	Findings																	

M = male  
F = female

C = cervix  
\* = viable foetuses are identified by assigned foetal number

**A P P E N D I X      V I      IPPD : ORAL GAVAGE TERATOLOGY STUDY IN THE RAT  
(contd)      INDIVIDUAL CAESARIAN AND MACROSCOPIC FOETUS  
NECROPSY FINDINGS**

**GROUP: 4**

Dose Number	Parameter	Implantation Number															
		Left Horn of Uterus			Right Horn of Uterus												
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
88 (contd)	Implant Type*	17	18	19													
	FWT (g)	3.67	3.90	3.71													
	Sex	F	H	H													
	Findings																
89 (contd)	Implant Type*	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16
	FWT (g)	3.10	3.54	3.55	3.70	3.94	4.02	3.66	3.35	3.88	3.66	3.20	3.63	3.29	4.95	4.01	3.74
	Sex	F	F	H	F	H	H	F	F	H	H	F	H	F	H	H	
	Findings																
89 (contd)	Implant Type*	17	18	19	20	21	22										
	FWT (g)	3.89	3.80	3.35													
	Sex	F	F	H													
	Findings																
90 (contd)	Implant Type*	V1	V2	ED	C	LD	V3	V4	V5	V6							
	FWT (g)	3.27	3.52														
	Sex	H	F														
	Findings																
91	Implant Type*	V1	V2	V3	C	V4	V5	V6	V7	V8	V9	V10					
	FWT (g)	4.21	4.31	4.31	3.87	4.05	4.09	4.35	3.73	3.84	3.76						
	Sex	F	H	F	F	-	F	F	H	F	H						
	Findings																

M = male  
ED = early death

F = female  
FWT = foetal weight

C = cervix  
\* = viable foetuses are identified by assigned foetal number

LD = late death

A P P E N D I X  
 (contd)

V I INDIVIDUAL CAESARIAN AND MACROSCOPIC FOETUS  
 NECROPSY FINDINGS

GROUP: 4

DOSE LEVEL (mg/kg): 125																		
Dose Number	Parameter	Implantation Number																
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	
	Implant Type*	V1	V2	V3	V4	V5	V6	V7	V8	C	V9	V10	V11	V12	V13	V14	V15	V16
	FWT (g)	3.94	4.59	4.37	4.04	4.26	4.67	4.27	4.56	4.35	4.25	4.18	4.58	4.14	4.21	4.10	4.19	
92	Sex	F	H	F	F	H	H	F	H	F	F	F	H	F	F	F	F	
	Findings																	
	Implant Type*	V17	V18															
	FWT (g)	4.22	3.78															
92	Sex	F	F															
	Findings																	
	Implant Type*	V1	V2	V3	V4	V5	V6	V7	C	V8	V9	V10	V11	V12	V13	V14	V15	
	FWT (g)	3.33	2.88	3.51	3.43	3.36	3.73	3.73	3.57	3.52	3.86	3.33	3.27	3.24	3.30			
93	Sex	F	F	H	F	F	H	H	H	F	H	F	F	F	F			
	Findings																	
	Implant Type*	V1	V2	V3	V4	V5	C	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	
	FWT (g)	4.43	4.15	4.31	4.43	4.36	4.72	4.01	4.37	4.05	4.21	4.02	4.52	4.12	3.92			
94	Sex	H	F	F	H	F	H	F	H	H	F	H	F	H	H	F		
	Findings																	
	Implant Type*	V1	V2	V3	V4	V5	C	V6	V7	V8	V9	C	V10	V11	V12	V13	V14	
	FWT (g)	3.02	3.34	3.29	3.04	3.27	3.61	3.46	3.62	3.57	3.60	3.35	3.60	3.66	3.50	3.66	3.15	
95	Sex	F	H	H	F	F	H	H	F	F	H	H	F	H	H	F		
	Findings																	

M = male  
 F = female  
 FWT = foetal weight

\* = viable foetuses are identified by assigned foetal number

C = cervix

A P P E N D I X VI  
INDIVIDUAL CAESARIAN AND MACROSCOPIC FOETUS  
NECROPSY FINDINGS  
(contd)

GROUP: 4

Dam Number	Parameter	Implantation Number															
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
95	Implant Type*	17	18	19													
	FWT (g)	3.24	3.40	3.02													
	Sex	H	H	H													
	Findings																
96	Implant Type*	V1	V2	V3	V4	V5	V6	V7	V8	C	V9	V10	V11	V12	V13	V14	V15
	FWT (g)	3.67	3.50	4.25	3.98	4.22	4.16	3.90	3.90	4.09	3.77	3.92	4.01	4.13	4.02	4.18	
	Sex	F	F	H	H	H	H	H	H	F	F	F	F	F	H	H	
	Findings																
	Implant Type*	17															
	FWT (g)	V16															
	Sex	3.85															
	Findings	H															

H = male  
EP = early death

F = female  
FWT = foetal weight

C = cervix  
\* = viable foetuses are identified by assigned foetal number

## APPENDIX VII

### INDIVIDUAL FOETUS VISCERAL FINDINGS

#### KEY TO OBSERVATIONS

##### Head

- a = unilateral microphthalmia
- aa = unilateral retinal infolding
- b = ovoid lens(es) of eye(s)
- c = enlarged brain ventricle(s)/collecting duct
- d = blood in nasal passages
- e = haemorrhage within meningeal tissues
- f = haemorrhage in back of brain/pituitary area
- g ♂ subcutaneous haemorrhage on head

##### Neck/Thorax

- h = undescended lobe(s) of thymus
- i = blood in oesophagus and/or trachea
- j = short brachiocephalic trunk
- k = no brachiocephalic trunk
- l = pericardial oedema
- m = interventricular septal defect
- n = right sided aorta, aortic arch and ductus arteriosus
- o = left atrium and mitral valve atretic
- p = no pulmonary trunk, modified ductus arteriosus (exits from right ventricle)

##### Abdomen

- q = unilateral/bilateral small/no development of renal papilla(e)
- r = unilateral/bilateral increased renal pelvic cavitation
- s = unilateral/bilateral kinked and/or dilated ureter(s)
- t = unilateral/bilateral dark adrenal medulla(e)
- u = unilateral dark adrenal
- v = unilateral small adrenal
- w = immature liver
- x = extra lobulation of liver median lobe
- y = blood/haemorrhage in abdomen

APPENDIX VII (contd) INDIVIDUAL FOETUS VISCERAL FINDINGS

GROUP: 1 DOSE LEVEL (mg/kg): 0

Dam Number	Number of Foetuses Examined	Number of Affected Foetuses	% of Foetuses Affected	Foetus Identity	Findings
1	8	5	62.5	3	h
2	7	3	42.9	1	b
3	10	2	20.0	3	h
4	10	3	30.0	9	h,s
				15	h
				1	c
				11	q
				13	q
				15	h
				11	r,s
				17	b,q

APPENDIX VIII (contd) INDIVIDUAL FOETUS VISCERAL FINDINGS

GROUP: 1 DOSE LEVEL (mg/kg): 0

Dam Number	Number of Foetuses Examined	Number of Affected Foetuses	% of Foetuses Affected	Foetus Identity	Findings
5	7	5	71.4	3	q
6	6	1	16.7	5	q
7	7	2	28.6	5	q
8	4	1	25.0	5	q,s
9	7	2	28.6	7	h
10	9	6	66.7	1	q,r,s
				3	h
				5	q,s
				7	s
				9	v
				11	h

APPENDIX VIII (contd) INDIVIDUAL FOETUS VISCERAL FINDINGS  
IPPD : ORAL GAVAGE TERATOLOGY STUDY IN THE RAT

GROUP: 1		DOSE LEVEL (mg/kg): 0			
Dam Number	Number of Foetuses Examined	Number of Affected Foetuses	% of Foetuses Affected	Foetus Identity	Findings
11	4	1	25.0	7	q,s
12	9	0	0.0	-	-
13	9	6	66.7	1	q,q,s
				3	q,s
				5	q,s
				7	s
				9	q,s
				11	e,q,s
14	8	1	12.5	5	a,k,m,n,o,p
15	10	2	20.0	15	w
16	8	1	12.5	19	q,s
17	9	2	22.2	15	h
				3	x
				11	x

APPENDIX VIII (contd) INDIVIDUAL FOETUS VISCERAL FINDINGS

GROUP: 1

DOSE LEVEL (mg/kg): 0

Dam Number	Number of Foetuses Examined	Number of Affected Foetuses	% of Foetuses Affected	Foetus Identity	Findings
18	8	3	37.5	1	q,r,s
19	6	2	33.3	3	q
20	8	2	25.0	1	q,s
21	7	3	42.9	13	x
					x
22	10	2	20.0	7	q,s
23	7	5	71.4	5	q
					h
24	9	1	11.1	9	h
					q,r,s,y
					q,s
					h,q,s
					h
					q,r,s

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APPENDIX VIII (contd)      INDIVIDUAL FOETUS VISCERAL FINDINGS

GROUP: 2

Dam Number	Number of Foetuses Examined	Number of Affected Foetuses	% of Foetuses Affected	Foetus Identity		Findings
				F	S	
25	5	4	80.0	1	3	q, s
26	9	2	22.2	5	13	q, s
27	7	1	14.3	11	c	h
28	8	3	37.5	3	5	aa
				7	11	h
29	5	1	20.0	9	q, s	
30	8	1	12.5	5	q, s	
31	9	4	44.4	1	i	q
				5	11	q
				13	13	q

APPENDIX VII (contd)    INDIVIDUAL FOETUS VISCERAL FINDINGS

GROUP: 2

DOSE LEVEL (mg/kg): 12.5

Dam Number	Number of Foetuses Examined	Number of Affected Foetuses	% of Foetuses Affected	Foetus Identity	Findings
32	8	7	87.5	1	h x
33	9	4	44.4	3	b,h h q h 15
34	5	3	60.0	3	h,q,r,s q,s q,s b b,q
35	7	2	28.6	5	q,s q 13
36	8	2	25.0	1	h h,x
37	9	1	11.1	11	s

APPENDIX VIII (contd) INDIVIDUAL FOETUS VISCERAL FINDINGS

GROUP: 2	Dam Number	Number of Foetuses Examined	Number of Affected Foetuses	% of Foetuses Affected	Foetus Identity	Findings	DOSE LEVEL (mg/kg): 12.5
38	8	3	3	37.5	3	q,s q h	
39	8	4	50.0	1	5	q,r,s x q h,x	
40	9	2	22.2	7	11	q,r,s q,s	
41	9	3	33.3	1	11	q s	
42	10	4	40.0	7	11	h x q w	
43	6	2	33.3	3	5	b,g,h h,s	
44	10	3	30.0	7	9	h,m q,s l	

APPENDIX VIII (contd) INDIVIDUAL FOETUS VISCERAL FINDINGS

IPPO : ORAL GAVAGE TERATOLOGY STUDY IN THE RAT

GROUP: 2 DOSE LEVEL (mg/kg): 12.5

Dam Number	Number of Foetuses Examined	Number of Affected Foetuses	% of Foetuses Affected	Foetus Identity	Findings
45	8	1	12.5	11	y
46	8	0	0.0	-	-
47	8	3	37.5	3	x b,x t
48	8	4	50.0	1 5 7 13	h h x q,r,s

APPENDIX VIII (contd) INDIVIDUAL FOETUS VISCERAL FINDINGS

GROUP: 3

Dam Number	Number of Foetuses Examined	Number of Affected Foetuses	% of Foetuses Affected	Foetus Identity		Findings
				Identity	Findings	
49	8	3	37.5	3	q,s	
50	3	1	33.3	7	x	
51	8	6	75.0	13	q	b
				1	q	
				3	q	
				5	h	
				11	aa	
				13	q,s	
				15	q	
52	8	2	25.0	1	c,q,r,s	
53	8	6	75.0	15	q	
				1	b,c,w	
				3	b,q	
				5	s	
				9	h	
				13	x	
				15	b	

APPENDIX VIII (contd) INDIVIDUAL FOETUS VISCERAL FINDINGS

GROUP: 3	Dose Level (mg/kg): 62.5	Dam Number	Number of Foetuses Examined	Number of Affected Foetuses	% of Foetuses Affected	Foetus Identity	Findings
54		9	2	2	22.2	7	q,s q
55		11	4	3	36.4	3	h q
						11	h
						17	s
56		6	2	2	33.3	1	s b,h
57		4	3	3	75.0	1	q
						3	x
58		8	6	6	75.0	5	b
						1	q,s b
						3	c,q j,q,s
						9	q
						11	j,q,s
						13	q
						15	q

**APPENDIX VIII (contd) INDIVIDUAL FOETUS VISCERAL FINDINGS**

**GROUP: 3**

**DOSE LEVEL (mg/kg): 62.5**

Dam Number	Number of Foetuses Examined	Number of Affected Foetuses	% of Foetuses Affected	Foetus Identity	Findings
59	7	5	71.4	1	q,r,s
60	7	1	14.3	1	q,s
61	6	0	0.0	-	-
62	7	2	28.6	3	b
63	8	1	12.5	11	q,s
64	2	1	50.0	1	q,s
65	8	4	50.0	1	h,q,s,x
66	9	- 2	22.2	5	h
				7	s

APPENDIX VII (contd) INDIVIDUAL FOETUS VISCERAL FINDINGS  
IPPD : ORAL GAVAGE TERATOLOGY STUDY IN THE RAT

GROUP: 3	Dose Level (mg/kg): 62.5	Dam Number	Number of Foetuses Examined	Number of Affected Foetuses	% of Foetuses Affected	Foetus Identity	Foetal Findings
67		6	6	100.0	1	x	x
68		7	1	14.3	3	q,s,x	b,q,x
69		7	2	28.6	1	a,b,q,r,s	h
70		9	3	33.3	1	b,c,q,s	s
71		8	1	12.5	1	h,u	h
72		8	2	25.0	3	q	q

APPENDIX VII (contd) INDIVIDUAL FOETUS VISCERAL FINDINGS

GROUP: 4

		DOSE LEVEL (mg/kg): 125		
Dam Number	Number of Foetuses Examined	Number of Affected Foetuses	% of Foetuses Affected	Foetus Identity Findings
73	9	5	55.6	b,q,s b
74	10	3	30.0	7 9 13 q h
76	8	4	50.0	1 11 1 1 s
77	8	1	12.5	13 q
78	7	2	28.6	3 13 c,q
79	8	5	62.5	1 5 7 9 11 q,s q,s q,s q,s q,s

APPENDIX VIII (contd) INDIVIDUAL FOETUS VISCERAL FINDINGS

		DOSE LEVEL (mg/kg): 125		
Dam Number	Number of Foetuses Examined	Number of Affected Foetuses	% of Foetuses Affected	Foetus Identity
80	10	6	60.0	1 3 9 11 13 <b>b,q,s,x</b>
81	9	2	22.2	13 15 <b>x</b>
82	7	5	71.4	3 7 9 11 13 <b>b,q</b>
83	9	1	11.1	13 <b>h</b>
84	8	0	0.0	-
85	9	1	11.1	13 <b>h</b>
86	8	0	0.0	-

IPPD : ORAL GAVAGE TERATOLOGY STUDY IN THE RAT

APPENDIX VIII (contd) INDIVIDUAL FOETUS VISCERAL FINDINGS

GROUP: 4

Dam Number	Number of Foetuses Examined	Number of Affected Foetuses	% of Foetuses Affected	Foetus Identity	DOSE LEVEL (mg/kg): 125		
					Findings	Findings	Findings
87	8	3	37.5	7	h	e	
				9	f,h		
				13			
88	10	8	80.0	1	q,s		
				7	h,q,s		
				9	b,h,q,r,s		
				11	q,r		
				13	h		
				15	h,s		
				17	q,s		
				19	h		
89	11	7	63.6	1	h,q		
				3	q,s		
				5	h		
				7	s		
				13	h		
				19	q		
90	3	0	0.0	21	q		

APPENDIX VIII (contd) INDIVIDUAL FOETUS VISCERAL FINDINGS

GROUP: 4	DOSE LEVEL (mg/kg): 125				
Dam Number	Number of Foetuses Examined	Number of Affected Foetuses	% of Foetuses Affected	Foetus Identity Findings	
91	5	1	20.0	7	x
92	9	5	55.6	5	s,x
				9	s
				11	s
				13	s
93	7	2	28.6	9	q
94	7	0	0.0	-	x
95	10	8	80.0	1	q,s
				3	q,s
				7	q,s
				9	q
				11	r
				13	q,r,s
				15	q,x
				19	q
96	8	6	75.0	1	h
				3	h
				5	h
				7	h
				11	q
				13	q

APPENDIX VIII INDIVIDUAL FOETUS SKELETAL DEVELOPMENT  
IPPD : ORAL GAVAGE TERATOLOGY STUDY IN THE RAT

GROUP: 1

DOSE LEVEL (mg/kg): 0

Dam Number	Number of Foetuses Examined	Number of Ribs 13/13 13/14 14/14	Number of Fully Ossified Sternum 4 4 24	Number of Vertebral Centra 27	Number of Post Lumbar Vertebrae 5	Number of Vertebral Arches 25	Fontanelle Size	Metacarpals/Metatarsals	Small Medium Large 6/6 6/8 8/8
1	7	5	2	1	2	4	1	6	1
2	7	6	1	2	5	7	2	5	6 1
3	10	9	1	8	2	8	10	10	10
4	9	6	3	7	2	9	9	1	8
5	7	4	3	1	5	1	7	6	7
6	6	6	6	1	5	6	1	5	4 2
7	6	6	6	2	2	1	3	1	6
8	4	4	4	2	2	1	3	4	4
9	7	6	1	7	7	1	6	2	5
10	8	8	8	1	7	8	8	7	1 1
11	3	3	3	3	3	3	1	2	3
12	9	7	2	1	5	3	9	1	8 9

IPPD : ORAL GAVAGE TERATOLOGY STUDY IN THE RAT

APPENDIX VII INDIVIDUAL FOETUS SKELETAL DEVELOPMENT  
(contd)

GROUP: 1

DOSE LEVEL (mg/kg): 0

Dam Number	Number of Foetuses Examined	Number of Ribs 13/13 13/14 14/14	Number of Fully Ossified Sternebrae <4 4 24	Number of Vertebral Centra <7 7 27	Number of Post Lumbar Vertebrae <5 25	Number of Vertebral Arches >5 25	Number of Fontanellae			
							Post Lumbar	Vertebral Centra	Vertebrae >5	Fontanelle Size
							Small	Medium	Large	
13	8	7	1	2	6	8	8	1	7	8
14	7	7		7	7	7		7	1	6
15	9	6	3	2	7	9	9	4	5	9
16	8	8		2	6	8		8	7	1
17	8	8		6	2	1	1	7	8	8
18	8	8		3	4*	8	3	5	7	1
19	5	5		4	1	5	5	5	5	1
20	7	7		4	3	7	7	7	7	7
21	7	7		6	1	1	6	5	2	7
22	9	7	2	1	8	9	9	2	2	7
23	6	5	1	1	5	6	6	3	3	2
24	9	8		1	1	6	2	2	7	3
							6	6	9	9

\* = one foetus damaged - unable to evaluate this parameter

IPPD : ORAL GAVAGE TERATOLOGY STUDY IN THE RAT

A P P E N D I X      V I T I      INDIVIDUAL FOETUS SKELETAL DEVELOPMENT  
(contd)

GROUP: 2

DOSE LEVEL (mg/kg): 12.5

Dam Number	Number of Foetuses Examined	Number of Ribs	Number of Ossified Sternebrae	Number of Fully Ossified Vertebrae	Number of Post Lumbar Vertebral Centra	Number of Post Lumbar Vertebral Arches	Number of Metacarpals / Metatarsals	Fontanelle Size	Number of Small Medium Large
25	5	5	5	5	5	5	5	5	5
26	8	3	2	3	8	8	8	3	5
27	6	5	1	2	4	6	6	6	6
28	8	6	2	8	8	8	3	5	7
29	4	4	3	1	4	3	1	4	4
30	7	4	2	1	7	7	1	6	4
31	8	8	2	4	2	8	1	7	8
32	7	7	7	7	7	6	1	7	7
33	8	8	5	3	3	5	3	1	6
34	4	4	1	1	2	4	1	3	3
35	7	7	4	3	7	7	7	6	1
36	7	5	1	1	3	4	7	1	2

\* = one foetus damaged - unable to evaluate this parameter

IPPD : ORAL GAVAGE TERATOLOGY STUDY IN THE RAT  
APPENDIX VII INDIVIDUAL FOETUS SKELETAL DEVELOPMENT  
(contd)

GROUP: 2 (contd)

DOSE LEVEL (mg/kg): 12.5

Dam Number	Foetuses Examined	Number of Ribs	Number of Ossified Sternum	Fully Vertebral Centra	Post Lumbar Vertebrae	Post Lumber Arches	Number of Metacarpals / Metatarsals	Fontanelle Size	Number of Small Medium Large
37	6	6	1	1	1	1	1	7	1
38	6	7	1	8	8	8	1	7	8
39	6	8	7	1	2	6	3	5	6+
40	9	9	1	8	9	9	9	9	1
41	9	8	1	2	6*	9	9	1	3
42	9	9	1	8	9	1	8	1	4
43	5	5	2	2*	5	5	5	5	5
44	10	10	3	6*	1	9	1	9	7
45	7	5	2	2	5	7	7	5	1
46	8	7	1	2	6	8	2	6	8
47	7	5	1	1	6	1	6	2	7
48	8	7	1	5	3	8	8	8	8

\* = one foetus damaged - unable to evaluate this parameter  
+ = two foetuses damaged - unable to evaluate this parameter

APPENDIX VII  
INDIVIDUAL FOETUS SKELETAL DEVELOPMENT  
(contd)

GROUP: 3

DOSE LEVEL (mg/kg): 62.5

Dam Number	Number of Foetuses Examined	Number of Ribs 13/13 13/14 14/14	Number of Fully Ossified Sternebrae 44 4 24	Number of Post Lumbar Vertebral Centra 47 27	Number of Post Lumbar Vertebrae Arches 25	Number of Fontanellae Metacarpals / Metatarsals				
						0/0	5/6	6/6	6/8	7/8
49	7	7	1	6	7	7		4	3	7
50	2	1	1	1	1	1	1	1		2
51	7	6	1	7	7	7		6	1	7
52	8	6	1	2	6	7*	2	5*		8
53	7	6	1	1	6	4	3	7		7
54	8	8	3	5	8	2	6		5	4
55	10	9	1	1	6	3	2	8	2	10
56	6	5	1	1	5	6	6		4*	1
57	3	3	1	2	1	2	3		2	1
58	7	7	1	4	2	7	2	5		7
59	6	6	1	5	1	5	3	3	6	2
60	7	6	1	1	6	7	1	6	1	6
										7

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PROJECT NUMBER: 543/2

\* = one foetus damaged - unable to evaluate this parameter

IPPD : ORAL GAVAGE TERATOLOGY STUDY IN THE RAT

APPENDIX VIII INDIVIDUAL FOETUS SKELETAL DEVELOPMENT  
(contd)

GROUP: 3 (contd)

Dam Number	Number of Foetuses Examined	Number of Ribs	Number of Vertebrae	Post Lumber Vertebrae Centra	Number of Arches	Number of Fontanelle Size			Number of Metacarpals / Metatarsals			Fontanelle Size		
						44	46	47	27	25	6/6	6/8	7/8	8/8
61	7	7	7	1 6	7	1	6			5	1	1	1	6
62	7	6	1	7	7	7				5	2			7
63	8	8	1	5 2	1 7	1	7			8			6	2
64	1	1	1	1	1	1				1			1	
65	7	7	1	6	7	7				6	1		1	6
66	9	9	1	8	9	9				3	1	5	2	7
67	5	4*	1 1	1+ 2	3	1	4			1	4		5	
68	7	7	2	5	7	1	6			3	4		2	5
69	7	6	1	1 6	7	7				6	1		7	
70	9	7	2	2 7	9	3	6			9			9	
71	7	4	1	2	5 2	7				7	6	1	7	
72	7	7	1	4 2	7	7				7			7	

\* = one foetus damaged - unable to evaluate this parameter  
+ = two foetuses damaged - unable to evaluate this parameter

IPPD : ORAL GAVAGE TERATOLOGY STUDY IN THE RAT

A P P E N D I X      V I I I      INDIVIDUAL FOETUS SKELETAL DEVELOPMENT  
(contd)

GROUP: 4

DOSE LEVEL (mg/kg): 125

Dam Number	Number of Foetuses Examined	Number of Ribs 13/13 13/14 14/14	Number of Fully Ossified Sternebrae <4 4 >4	Number of Vertebral Centra <7 7 >7	Number of Post Lumbar Vertebrae Arches <5 5 >5	Number of Post Lumbar Vertebrae Arches			Number of Metacarpals / Metatarsals			Fontanelle Size		
						6/6	6/7	6/8	7/8	8/8	Small	Medium	Large	
73	9	8	1	4	5	2	7	4	5	5	4	4	9	
74	10	9	1	2	8	10	10	9	9	1	1	10		
76	8	8		7	1	2	6	4	4	1	1	2	8	
77	8	4	2	2	5	3	1	7	3	5	8	8		
78	7	4	1	2	2	5	7	2	5	1	1	5	7	
79	8	6	2	2	6	6	8	8	8	1	7	3	5	
80	9	9		1	3	5	1	8	9	1	8	1	8	
81	9	6	3	5	4	9	1	8	1	5	4	9		
82	7	6		1	3	4	7	2	5	5	1	1	7	
83	9	5	1	3	2	7	9	1	8	7	1	1	9	
84	7	7		3	4	7	7	7	7	1	6	7		

APPENDIX VIII INDIVIDUAL FOETUS SKELETAL DEVELOPMENT  
(contd)

GROUP: 4 (contd)

DOSE LEVEL (mg/kg): 125

Dam Number	Number of Foetuses Examined	Number of Ribs 13/13 13/14 14/14	Number of Fully Ossified Sternebrae <4 4 >4	Number of Post Lumbar Vertebral Centre <7 7 >7	Number of Arches <5 5 >5	Number of Metacarpals / Metatarsals			Number of Fontanelle Size		
						6/6	6/7	6/8	7/8	8/8	Small
85	9	9		2 7	9	9			2	7	9
86	8	8		6 2	6	1 7			1	7	8
87	7	7		2 5	7	1 6			5	2	7
88	9	9		1 3 5	1 8	1 8			9		9
89	10	10		2 8	10	10	2	7	1	10	
90	3	1	1	1 2	3	3			1	2	3
91	5	4	1	2 3	5	5			4	1	5
92	9	8	1	9	9	9			2	7	4
93	7	6	1	6 1	6*	6*			6*		7
94	7	4	3	1 6	7	7			4	1	2
95	9	9		1 8	9	2 7			8	1	9
96	8	7	1	5 3	8	1 7			7	1	8

\* = one foetus damaged - unable to evaluate this parameter

APPENDIX IX

INDIVIDUAL FOETUS SKELETAL FINDINGS

KEY TO OBSERVATIONS

Head/Neck

- a - incomplete ossification of one cranial bone
- b - incomplete ossification of more than one cranial bone
- c - incomplete ossification of one facial bone
- d - incomplete ossification of more than one facial bone
- e - irregular ossification of one cranial bone
- f - irregular ossification of more than one cranial bone
- g - irregular ossification of one facial bone
- h - irregular ossification of more than one facial bone
- i - no ossification of one cranial bone
- j - incomplete ossification of hyoid
- k - irregular ossification of hyoid
- l - no ossification of hyoid
- m - incomplete ossification of basisphenoid
- n - enlarged frontal/nasal suture
- o - mis-shapen frontals and parietals

Pectoral Girdle

- p = incomplete ossification of scapula

Ribs

- q = unilateral/bilateral rudimentary 13th rib(s)
- r - unilateral/bilateral rudimentary 14th rib(s)
- s = unilateral/bilateral short rib(s) - excludes 14th ribs
- t = bilateral short 14th ribs
- u = unilateral/bilateral wavy rib(s)
- v = bilateral thickened ribs
- w = bilateral incompletely ossified ribs

APPENDIX IX (contd)

Sternebrae

x = one sternebra incompletely ossified  
y = more than one sternebra incompletely ossified  
z = one sternebra not ossified  
aa = more than one sternebra not ossified  
bb = one sternebra small  
cc = more than one sternebra small  
dd = one sternebra semi-bipartite  
ee = more than one sternebra bipartite  
ff = one sternebra misaligned  
gg = more than one sternebra misaligned  
hh = one sternebra assymetric

Vertebrae

ii = one thoracic vertebral centrum semibipartite  
jj = more than one thoracic vertebral centrum semi-bipartite  
kk = one thoracic vertebral centrum bipartite  
ll = more than one thoracic vertebral centrum bipartite  
mm = atlases short  
nn = bilateral incomplete ossification of lumbar arches

Pelvic Girdle

oo = incomplete ossification of pubis(es)  
pp = irregular ossification of pubis(es)  
qq = no ossification of pubes  
rr = small/short pubes  
ss = incomplete ossification of ischium(a)  
tt = no ossification of ischia  
uu = short ischium  
vv = incomplete ossification of illia  
ww = pelvic shift - 27 pre sacral vertebrae

Hind Limbs

xx = no ossification of femurs  
yy = incomplete ossification of tibiae and fibulae

APPENDIX IX (contd)                    IPPD : ORAL GAVAGE TERATOLOGY STUDY IN THE RAT  
    INDIVIDUAL FOETUS SKELETAL FINDINGS

GROUP: 1                                    DOSE LEVEL (mg/kg): 0

Dam Number	Number of Foetuses Examined	Number of Affected Foetuses	% of Foetuses Affected	Foetus Identity	Findings
1	7	2	28.6	4	r f,r,u,y,z
2	7	2	28.6	2	r
3	10	2	20	10	a,l
4	9	5	55.6	12	r
				14	a,j
5	7	7	100	4	b a,ii,00 b,d,i,z,jj,qq
				6	a,l,r
				8	b,h,r,ii,00
				10	a,jj
				12	b,00
				14	r

APPENDIX IX (contd)      INDIVIDUAL FOETUS SKELETAL FINDINGS

GROUP: 1 (contd)		DOSE LEVEL (mg/kg): 0			
Dam Number	Number of Foetuses Examined	Number of Affected Foetuses	% of Foetuses Affected	Foetus Identity	Findings
6	6	4	66.7	2	1 11
7	6	1	16.7	4	99
8	4	2	50	10	z
9	7	4	57.1	12	a
10	8	2	25	10	b, 1
11	3	0	0	12	a
					-

APPENDIX IX (contd)                    IPPD : ORAL GAVAGE TERATOLOGY STUDY IN THE RAT

INDIVIDUAL FOETUS SKELETAL FINDINGS

GROUP: 1 (contd)                    DOSE LEVEL (mg/kg): 0

Dam Number	Number of Foetuses Examined	Number of Affected Foetuses	% of Foetuses Affected	Foetus Identity	Findings
12	9	4	44.4	2	a,r,z a,r,bb 1 b,d
13	8	2	25	2 14	b,h,j r
14	7	0	0	-	-
15	9	3	33.3	8 14 18	r r r
16	8	4	50	6 12 14 16	ee ii 1,00 b,c,1
17	8	3	37.5	2 10 16	q,s a,l e

APPENDIX IX (contd)            INDIVIDUAL FOETUS SKELETAL FINDINGS

GROUP: 1 (contd)		DOSE LEVEL (mg/kg): 0			
Dam Number	Number of Foetuses Examined	Number of Affected Foetuses	% of Foetuses Affected	Foetus Identity	Findings
18	8	6	75	2	a 1
				8	b
				10	a,bb
				12	j
				14	a
				16	
19	5	2	40	8	a 1
20	7	2	28.6	2	a
21	7	4	57.1	4	a,rr a, b, j
22	9	3	33.3	2	a, b, j
				10	r
				12	j
				16	r

APPENDIX IX (contd)      IPPD : ORAL GAVAGE TERATOLOGY STUDY IN THE RAT  
INDIVIDUAL FOETUS SKELETAL FINDINGS

GROUP:	2	DOSE LEVEL (mg/kg): 12.5		
Dam Number	Number of Foetuses Examined	Number of Affected Foetuses	% of Foetuses Affected	Foetus Identity Findings
23	6	1	16.7	8 r
24	9	7	77.8	2 a 4 b,h,l,x,ii,oo 8 c 10 r 14 l,z 16 l 18 a,l,ii
25	5	1	20	8 a
26	8	5	62.5	2 r 6 r 8 r 12 r 14 r
27	6	1	16.7	6 r

## APPENDIX IX (contd)

IPPD : ORAL GAVAGE TERATOLOGY STUDY IN THE RAT  
INDIVIDUAL FOETUS SKELETAL FINDINGS

GROUP: 2

Dam Number	Number of Foetuses Examined	Number of Affected Foetuses	% of Foetuses Affected	DOSE LEVEL (mg/kg): 12.5	
				Foetus Identity	Findings
28	8	4	50	2	h
				4	r
				12	kk
				14	r,ii
29	4	1	25	4	b,1
30	7	5	71.4	2	1,ii
				6	ii
				8	j,r
				10	a,j,r,ii
				14	1,r

APPENDIX VII INDIVIDUAL FOETUS SKELETAL DEVELOPMENT

IPPD : ORAL GAVAGE TERATOLOGY STUDY IN THE RAT

GROUP: 1

Dam Number	Number of Foetuses Examined	Number of Ribs 13/13 13/14 14/14	Fully Ossified Sternebrae <4 4 >4	Number of Post Lumbar Vertebral Centra <7 7 >7	Number of Post Lumbar Arches <5 5 >5	Number of Fontanelle		
						Post Lumbar	Metacarpals/ Metatarsals	Fontanelle Size
							Small	Medium Large
1	7	5	2	1 2 4	1 6	1 6	1	6
2	7	6	1	2 5	7	2 5	6	1
3	10	9	1	8 2	2 8	10	10	10
4	9	6	3	7 2	9	9	1	8
5	7	4	3	1 5 1	7	6 1	7	7
6	6	6	1	5	6	1 5	4	2
7	6	6	6	6	6	6	6	6
8	4	4	4	2 2	1 3	1 3	4	4
9	7	6	1	7	7	1 6	2	5
10	8	8	1	7	8	8	7	1
11	3	3	3	3	3	1 2	3	3
12	9	7	2	1 5 3	9	1 8	9	9

**APPENDIX IX (contd)**

**INDIVIDUAL FOETUS SKELETAL FINDINGS**

**GROUP: 2 (contd)**

DOSE LEVEL (mg/kg): 12.5					
Dam Number	Number of Foetuses Examined	Number of Affected Foetuses	% of Foetuses Affected	Foetus Identity	Findings
35	7	2	28.6	1	b,o a
36	7	2	28.6	4	r r
37	8	7	87.5	2	1 a,d,j,r b,d,e,g,j,m,n, p,r,aa,cc,hh, jj,kk,mm,qq, ss,ww b,d,h,l l,ii ii j
38	8	4	50	4	1,r b,g,l a,l a
39	8	5	62.5	2	a,ff a,l ff a,d,f,h,l a

## APPENDIX IX (contd)

IPPD : ORAL GAVAGE TERATOLOGY STUDY IN THE RAT  
INDIVIDUAL FOETUS SKELETAL FINDINGS

GROUP: 2

DOSE LEVEL (mg/kg): 12.5

Dam Number	Number of Foetuses Examined	Number of Affected Foetuses	% of Foetuses Affected	Foetus Identity	Findings
23	6	1	16.7	8	r
24	9	7	77.8	4	<sup>a</sup> <sup>b,h,l,x,ii,oo</sup> c
				8	r
				10	r
				14	<sup>l,z</sup>
				16	1
				18	<sup>a,l,ij</sup>
25	5	1	20	8	<sup>a</sup>
26	8	5	62.5	2	r
				6	r
				8	r
				12	r
				14	r
27	6	1	16.7	6	r

## APPENDIX IX (contd)

IPPD : ORAL GAVAGE TERATOLOGY STUDY IN THE RAT  
INDIVIDUAL FOETUS SKELETAL FINDINGS

## GROUP: 2 (contd)

Dam Number	Number of Foetuses Examined	Number of Affected Foetuses	% of Foetuses Affected	Foetus Identity	DOSE LEVEL (mg/kg): 12.5	
					Findings	Findings
45	7	3	42.9	6	a,l	
46	8	4	50	8 10	a,r r	
47	7	5	71.4	10 12 14 16	r a b,h,l a	
48	8	7	87.5	2 4 6 8 10 12 14	bb,ii bb,ii ii,ii c b,jj ii r	

## APPENDIX IX (contd)

## INDIVIDUAL FOETUS SKELETAL FINDINGS

IPPD : ORAL GAVAGE TERATOLOGY STUDY IN THE RAT

GROUP: 2 (contd)

DOSE LEVEL (mg/kg): 12.5

Dam Number	Number of Foetuses Examined	Number of Affected Foetuses	% of Foetuses Affected	Foetus Identity	Findings
40	9	6	66.7	2	jj e a, l, ii l a, g, l, ii a, l
41	9	6	66.7	2	a r a l l l
42	9	6	66.7	2	rr z, rr a, j bb, ii, rr l k
43	5	0	0	-	-
44	10	5	50	6	a kk a, d, g b, c, l l
				8	
				12	
				18	
				20	

**A P P E N D I X I X (contd)**

**INDIVIDUAL FOETUS SKELETAL FINDINGS**

**GROUP: 3 (contd)**

Dam Number	Number of Foetuses Examined	Number of Affected Foetuses	% of Foetuses Affected	DOSE LEVEL (mg/kg): 62.5	
				Foetus Identity	Findings
55	10	8	80	2	b,l,z b,h,l,r b,l
56	6	2	33.3	10 12	r a
57	3	0	0	-	-
58	7	4	57.1	-	-
59	6	6	100	2 4 8 14	b a b b,d,e,l,u,bb
				2 4 6 8 10 12	b,bb b,d b,c,j,x,oo b bb a

## APPENDIX IX (contd)

IPPD : ORAL GAVAGE TERATOLOGY STUDY IN THE RAT  
INDIVIDUAL FOETUS SKELETAL FINDINGS

## GROUP: 3 (contd)

		DOSE LEVEL (mg/kg): 62.5		
Dam Number	Number of Foetuses Examined	Number of Affected Foetuses	% of Foetuses Affected	Foetus Identity
60	7	6	85.7	jj d
61	7	4	57.1	h r,jj ii a,c,l,jj
62	7	4	57.1	j,ii a,l i
63	8	4	50	dd,ff,ii b,d,l r dd,ff,ii
64	1	0	0	-
65	7	1	14.3	bb x bb bb ii

APPENDIX IX (contd) IPPD : ORAL GAVAGE TERATOLOGY STUDY IN THE RAT  
INDIVIDUAL FOETUS SKELETAL FINDINGS

GROUP:	3 (contd)	DOSE LEVEL (mg/kg):	62.5		
Dam Number	Number of Foetuses Examined	Number of Affected Foetuses	% of Foetuses Affected	Foetus Identity	Findings
66	9	3	33.3	4	ii g,1,ii gg
67	5	2	40	2	b,y,aa,oo q
68	7	4	57.1	4	b,h ii ii c
69	7	1	14.3	6	r a,1,ii ii jj ii r,ii ii ii
70	9	9	100	2	6 8 10 12 14 16 18

IPPD : ORAL GAVAGE TERATOLOGY STUDY IN THE RAT  
APPENDIX IX (contd) INDIVIDUAL FOETUS SKELETAL FINDINGS

GROUP: 3 (contd)		DOSE LEVEL (mg/kg): 62.5			
Dam Number	Number of Foetuses Examined	Number of Affected Foetuses	% of Foetuses Affected	Foetus Identity	Findings
71	7	5	71.4	2	c,r ii r
72	7	3	42.9	2 4 10	b,1,bb a,gg 1

## APPENDIX IX (contd)

## IPPD : ORAL GAVAGE TERATOLOGY STUDY IN THE RAT

GROUP: 4

## INDIVIDUAL FOETUS SKELETAL FINDINGS

		DOSE LEVEL (mg/kg): 125		
Dam Number	Number of Foetuses Examined	Number of Affected Foetuses	% of Foetuses Affected	Foetus Identity Findings
73	9	7	77.8	a,h,j,pp a b,d,e,h,j,ii,pp r
74	10	7	70.0	12 14 16 18 ii b,e,h,l,ii,pp
76	8	8	100	4 6 8 10 12 14 16 b,d,l,s b,d,l,s,oo,ss b,d,l,s,u,nn, oo,ss b,d,l b,d,l,bb a,c, b,d,l j

IPPD : ORAL GAVAGE TERATOLOGY STUDY IN THE RAT

A P P E N D I X I X (contd) INDIVIDUAL FOETUS SKELETAL FINDINGS

GROUP: 4 (contd) DOSE LEVEL (mg/kg): 125

Dam Number	Number of Foetuses Examined	Number of Affected Foetuses	% of Foetuses Affected	Foetus Identity	Findings
77	8	6	75	4	a, r
78	7	5	71.4	8 10 12 14 16	r l, r, bb a, r b, l
79	8	7	87.5	2 4 6 8 12 14 16	ii, r a ii a, e, h, l, r a, g b, h, l g

APPENDIX IX (contd)      INDIVIDUAL FOETUS SKELETAL FINDINGS

GROUP: 4 (contd)      DOSE LEVEL (mg/kg): 125

Dam Number	Number of Foetuses Examined	Number of Affected Foetuses	% of Foetuses Affected	Foetus Identity	Findings
80	9	8	88.9	2	ii b,d,e,h,l,z 1,jj b,d,h,l
81	9	6	66.7	2 8 10 14 16 18	b,d,h,l b,h r r r a,ff
82	7	6	85.7	2 4 8 10 12 14	a,l a,l a,l,ff b,d,l r b,d,l

IPPO : ORAL GAVAGE TERATOLOGY STUDY IN THE RAT  
APPENDIX IX (contd) INDIVIDUAL FOETUS SKELETAL FINDINGS

GROUP: 4 (contd)	DOSE LEVEL (mg/kg): 125			
Dam Number	Number of Foetuses Examined	Number of Affected Foetuses	% of Foetuses Affected	Foetus Identity Findings
83	9	6	66.7	4 r 6 b,d,l,r 10 b,l 14 r 16 b,l,r 18 l
84	7	7	100	2 a,g 4 u 6 b,h,u 8 bb,i 10 g,u,j 12 j 14 b,d,cc,ii
85	9	2	22.2	4 ii 6 b,e,u
86	8	3	37.5	8 l 12 a 14 l

APPENDIX IX (contd)                    INDIVIDUAL FOETUS SKELETAL FINDINGS  
IPPD : ORAL GAVAGE TERATOLOGY STUDY IN THE RAT

GROUP: 4 (contd)

		DOSE LEVEL (mg/kg): 125		
Dam Number	Number of Foetuses Examined	Number of Affected Foetuses	% of Foetuses Affected	Foetus Identity
87	7	6	85.7	2 4 6 8 12 14 z
88	9	8	88.9	2 4 6 8 10 14 16 18
89	10	5	50	2 10 12 16 20
90	3	3	100	2 4 6

r  
i  
e,r,z,00

a,g  
a  
g  
h  
h  
z

z,ii,oo  
b,g,i  
a  
ii

a,l,u  
b,e,i  
b,i  
ii  
bb

r  
i  
e,r,z,00

APPENDIX IX (contd)      INDIVIDUAL FOETUS SKELETAL FINDINGS

IPPD : ORAL GAVAGE TERATOLOGY STUDY IN THE RAT

GROUP: 4 (contd)      DOSE LEVEL (mg/kg): 125

Dam Number	Number of Foetuses Examined	Number of Affected Foetuses	% of Foetuses Affected	Foetus Identity	Findings
91	5	3	60	2	a
92	9	5	55.6	4	a
				8	r
				10	a, l
				12	b, d, ii
				14	g, j
				16	a, j
				18	r
93	7	3	42.9	2	cc
				4	bb, jj
				14	r, bb
94	7	5	71.4	2	r, ii
				4	r
				8	r
				10	ii
				14	ii

IPPD : ORAL GAUGAGE TERATOLOGY STUDY IN THE RAT  
INDIVIDUAL FOETUS SKELETAL FINDINGS

APPENDIX IX (contd)

GROUP: 4 (contd) DOSE LEVEL (mg/kg): 125

Dam Number	Number of Foetuses Examined	Number of Affected Foetuses	% of Foetuses Affected	Foetus Identity	Findings
95	9	4	44.4	2	a, i
96	8	4	50	4	b, d, f, h, l, z, oo b, d, h, l, x i r ff, ii

APPENDIX X

STUDY TIME PLAN

	<u>Date</u>
Study Directors Approval	21/12/92
Sponsors Approval	15/01/93
Animals Arrived	14/04/93
Start of Mating Period	04/05/93
Start of Dosing	10/05/93
Necropsy Start	24/05/93
Study Completed	04/06/93

## APPENDIX XI

### CHEMICAL ANALYSIS OF TEST MATERIAL FORMULATIONS

#### METHOD OF ANALYSIS

##### Introduction

The Flexzone 3C concentration in the test samples was determined spectrophotometrically.

##### Samples

The test material formulations were diluted with methanol such that the final theoretical test material concentration was approximately 0.006 mg/ml.

##### Standards

Standard solutions were prepared in methanol at a nominal concentration of 0.006 mg/ml.

##### Procedure

The absorbance of standard and sample solutions was measured at 297 nm in 1 cm cells using methanol as the reference medium.

##### Homogeneity Determinations

It was apparent by visual inspection that the test material formulations were homogenous.

##### Stability Determinations

The test material formulations were sampled and analysed initially and then after storage at approximately 4°C in the dark for 10 days.

##### Verification of Test Material Formulations Concentrations

The test material formulations were sampled and analysed within 3 days of preparation.

APPENDIX XI (continued)

RESULTS

STABILITY OF TEST MATERIAL FORMULATIONS

NOMINAL CONCENTRATION (mg/ml)	CONCENTRATION FOUND INITIALLY (mg/ml)	CONCENTRATION FOUND AFTER STORAGE FOR 10 DAYS	
		(mg/ml)	(expressed as % of initial)
2.5	2.31	2.38	103
12.5	10.5	10.6	101
25	23.1	23.3	101

VERIFICATION OF CONCENTRATION OF WEEKLY TEST MATERIAL FORMULATIONS

WEEK NUMBER	NOMINAL CONCENTRATION (mg/ml)	CONCENTRATION FOUND (mg/ml)	CONCENTRATION EXPRESSED AS % OF NOMINAL
1	2.5	2.49	100
	12.5	12.8	102
	25	25.5	102
2	2.5	2.53	101
	12.5	11.9	95
	25	25.1	100
3	2.5	2.72	109
	12.5	13.1	105
	25	26.1	105

TEST MATERIAL FORMULATION CONCENTRATIONS OVER THE DOSING PERIOD

NOMINAL CONCENTRATION (mg/ml)	MEAN CONCENTRATION FOUND (mg/ml)	MEAN CONCENTRATION EXPRESSED AS % OF NOMINAL	RANGE (mg/ml)	RANGE EXPRESSED AS % OF NOMINAL
2.5	2.58	103	2.49 - 2.72	100 - 109
12.5	12.6	101	11.9 - 13.1	95 - 105
25	25.6	102	25.1 - 26.1	100 - 105

APPENDIX XII

CERTIFICATE OF ANALYSIS

PERFORMING LABORATORY:

Safepharm Laboratories Limited

TEST MATERIALS:

<u>Test Material Name</u>	<u>Safepharm Serial Number</u>
Flexzone 3C	120182
Santoflex IP	120184
Permanax IPPD	120311

LABORATORY PROJECT NUMBER:

543/3

STUDY:

Determination of Purity/Impurities

METHODS:

% Purity Gas Chromatography (area normalisation).  
Moisture Content - Gravimetric  
Sulphated Ash - Gravimetric

RESULTS:

<u>Test material</u>	<u>% Purity (GC area normalisation)</u>	<u>Moisture content (% w/w)</u>	<u>Sulphated ash (% w/w)</u>
Flexzone 3C	97.2	<0.05	<0.05
Santoflex IP	96.8	<0.05	<0.05
Permanax IPPD	95.9	<0.06	<0.05

SIGNED: ..... DATE: .....

D. M. MULLEE G.R.S.C.  
LABORATORY SUPERVISOR

-175-

PROJECT NUMBER: 543/1

P A R T   I I

IPPD:

PRELIMINARY ORAL GAVAGE TERATOLOGY STUDY

IN THE RAT

PROJECT NUMBER: 543/1



IPPD:

PRELIMINARY ORAL GAVAGE

TERATOLOGY STUDY IN THE RAT

SUMMARY

Groups of eight mated female Sprague-Dawley CD strain rats were dosed orally, by gavage, with IPPD from day six to fifteen of gestation inclusive. The dose levels were 10, 50 and 100 mg IPPD/kg bodyweight with a concurrent control group dosed with vehicle only.

Individual clinical observations, bodyweight and food consumption were recorded during the study. The females were killed on day twenty of gestation, examined macroscopically and the uterine contents examined. The number of corpora lutea, implantation number, position and type, foetal weights, foetal sex and external appearance were recorded.

RESULTS

Adults

At 100 mg/kg there were signs of post dosing salivation and lethargy in 5/8 animals with ptosis noted in one animal. At 50 mg/kg one animal showed signs of diarrhoea.

At 100 mg/kg there was a slight reduction in group mean food consumption over the period of day 6 to day 9 of gestation.

Litters

There were no treatment related effects on foetal parameters.

CONCLUSION

Treatment of pregnant females with IPPD at dose levels of up to 100 mg/kg/day resulted in slight maternal toxicity at 100 mg/kg/day only. There were no treatment related effects on pregnancy or foetuses at any dose level.

IPPD:

PRELIMINARY ORAL GAVAGE  
TERATOLOGY STUDY IN THE RAT

1. INTRODUCTION

The objective of this study was to investigate the effects of IPPD when administered orally, by gavage, to pregnant rats during the period of embryo organogenesis.

The study was designed to comply with Principle Regulatory Guidelines.

The study was conducted in accordance with the internationally accepted general principles of Good Laboratory Practice and Safepharm Standard Operating Procedures.

The in-life phase of this study was conducted between 16 March 1993 and 8 April 1993 (see Appendix VII).

2. TEST MATERIAL

2.1 Description, Identification and Storage Conditions

Three samples of test material were supplied as follows:

Sponsor's identification	:	Flexzone 3C
Chemical name	:	N-phenyl-N'-isopropyl-p-phenylene diamine
Batch number	:	02240
Date received	:	28 January 1993
Description	:	dark brown/grey flakes
Container	:	opaque plastic tub
Storage conditions	:	room temperature
Purity (%)*	:	97.2
Supplied by	:	Uniroyal Chemical Company Inc Elm Street Naugatuck Connecticut 06770

2. TEST MATERIAL (contd)

2.1 Description, Identification and Storage Conditions (contd)

Sponsor's identification : Santoflex IP  
Chemical name : N-isopropyl-N'-phenylparaphenylene diamine  
Batch number : 2F054  
Date received : 28 January 1993  
Description : grey flakes  
Container : opaque plastic jar  
Storage conditions : room temperature in the dark  
Purity (%)\* : 96.8  
Supplied by : Monsanto plc  
Corporation Road  
Newport  
Gwent NP9 0XF

Sponsor's identification : Permanax IPPD  
Chemical name : N-isopropyl-N'-phenyl-1,4-phenylene diamine  
Batch number : 0779211410001  
Date received : 17 February 1993  
Description : dark brown pellets  
Container : opaque plastic jar  
Storage conditions : room temperature  
Purity (%)\* : 95.9  
Supplied by : Akzo Chemicals BV  
Kilkade 7  
P.O. Box 117  
3300 AC Dordrecht  
Holland

Data related to the identity and stability of the test material are the responsibility of the sponsor.

\* Purity determined by Safepharm Laboratories Limited (See Appendix XII of the main teratology study).

At the sponsors request the sample with the highest purity (Flexzone 3C supplied by Uniroyal Chemical Company INC) was used for the preliminary and main teratology studies.

2. TEST MATERIAL (contd)

2.2 Method of Preparation

Prior to dose preparation, IPPD was ground into a powder using a pestle and mortar.

IPPD was dissolved in Polyethylene Glycol 400 (vehicle) daily by weighing an amount of the test material into a suitable container and adding vehicle to make the appropriate final volume. Intermediate and low dose formulations were prepared by diluting the initial formulation. Homogeneity was assured by mixing the formulations with a Silverson mixer/homogeniser.

2.3 Dose Levels and Administration

The dose levels are presented in the following table and were selected on the basis of recommendations of the sponsor.

GROUP NUMBER	GROUP DESCRIPTION	DOSE LEVEL (mg/kg)	DOSE CONCENTRATION (mg/ml)
1	Control	0	0
2	Low	10	2.5
3	Intermediate	50	12.5
4	High	100	25

The test material and vehicle were administrated using a plastic catheter and plastic syringe at a constant dose volume of 4 ml/kg bodyweight.

Oral gavage administration was chosen as it represents a route of potential human exposure.

2.4 Analysis of Dose Preparations

Prior to the start of the study a procedure was developed to prepare the test material for dose administration. These preparations were analysed for achieved concentration and stability. The results of these analyses were used to ensure the validity of dose preparation for the main teratology study.

The methods of analysis and the results of these analyses are presented in Appendix XI of the main teratology study.

### 3. TEST SYSTEM

#### 3.1 Specification

Forty three virgin female Sprague-Dawley CD strain rats were obtained from Charles River (U.K.) Limited, Manston, Kent. Additionally, twenty-five sexually mature male Sprague-Dawley CD strain rats were used for mating purposes only.

On arrival the animals were examined and found to be in good health. The age range of the females on arrival was 9 to 12 weeks. The females were acclimatised to the laboratory conditions for at least 14 days before mating.

#### 3.2 Justification

The rat was chosen for this study as it represents the species historically used for safety evaluation studies and is specified by the principle regulatory authorities.

#### 3.3 Husbandry

The animals were housed in a single air-conditioned room, providing at least 15 air changes per hour. The room was maintained to operate within a temperature range of 19 and 25°C and a relative humidity of 40 and 75%, with these conditions monitored on a daily basis. Deviations from these ranges were recorded in the project log. It was concluded that these variations did not adversely affect the outcome of this study. The lighting within the room was controlled to allow 12 hours of continuous light within a 24-hour period.

Upon arrival, the females were housed in groups of five in polypropylene cages with stainless steel grid floors and lids, suspended over paper-lined polypropylene trays. During the mating period females were transferred to a similar type of cage with a sexually mature male on a maximum two female : 1 male basis.

3. TEST SYSTEM (contd)

3.3 Husbandry (contd)

Following evidence of successful mating, the animals were caged individually in polypropylene cages with solid floors and stainless steel grid tops. Autoclaved sawdust was used as bedding material.

Throughout the study the animals were given pelleted diet (SQC Rat and Mouse Breeder Diet No. 3 Expanded, Special Diet Services Limited, Witham, Essex, U.K.) ad libitum.

The animals were given water from plastic bottles attached to each cage, ad libitum.

The diet and water were considered not to have contained any contaminants at a level which may have affected the outcome of this study.

4. PROCEDURES

4.1 Mating

Prior to mating, vaginal smears were taken from all females in order to assess the stage of the oestrous cycle. Only those females in proestrus or proestrus/early oestrus were mated on that day.

Females were housed with males on a 2 female : 1 male basis. The following morning each tray was checked for the presence of ejected copulation plugs. All females were checked for copulation plugs in situ, and then a vaginal smear was taken to check for the presence of sperm. Females showing evidence of sperm within the vaginal smear were separated from the male and designated day 0 of gestation. These females were replaced with previously unmated females. The total mating period for this study was 4 days.

4. PROCEDURES (contd)

4.2 Allocation

Immediately after mating the females were assigned to treatment groups using a randomisation procedure based on stratified bodyweight to ensure comparable group mean bodyweights for each treatment group. The weight range of females at allocation was 214 to 275 grams. The females were assigned to positions on the cage battery using a randomised block design.

4.3 Animal Identification

At allocation females were given a unique earmark for the study according to the assigned number for each dose group. Each cage was identified with a colour coded card containing information including project number, dose group and animal number, as follows:

DOSE GROUP	COLOUR* CODE	NUMBER OF ANIMALS ASSIGNED	ANIMAL IDENTIFICATION NUMBER
1	Buff	8	1 - 8
2	Green	8	9 - 16
3	Blue	8	17 - 24
4	Red	8	25 - 32

\* for cage cards and raw data sheets

4.4 Dosing

Mated female rats were dosed according to dose group, once daily from day six to fifteen of gestation, inclusive. The dose administered was adjusted for bodyweight on each day.

The study was not designed to show proof of test material absorption.

## 5. OBSERVATIONS

### 5.1 Morbidity/Mortality

All females were checked twice daily during the normal working week and once daily at weekends.

### 5.2 Clinical Observations

All females were observed once daily, in the morning throughout gestation and, additionally, one hour after dosing, throughout the dosing period, for clinical signs of toxicity.

### 5.3 Bodyweight

All females were weighed on days 0, 3, 6 to 15 inclusive, 18 and 20 of gestation.

### 5.4 Food Consumption

Food consumption for individual animals was recorded for discrete periods throughout the study on days 0-3, 3-6, 6-9, 9-12, 12-15, 15-18 and 18-20 of gestation.

### 5.5 Terminal Studies

All surviving females were killed on day 20 of gestation by carbon dioxide asphyxiation. Each animal was examined externally and internally for macroscopic abnormalities. The uterus of any apparently non-pregnant female was dissected free and subsequently stained with 10% ammonium polysulphide and examined for implantations (Salewski 1964). The ovaries and uteri of pregnant females were removed, examined and the following data recorded:

- i) Number of corpora lutea
- ii) Number, position and type of intrauterine implantation

Implantation types were divided into:

Early Death - No visible distinction between placental/decidual tissue and embryonic tissue.

5. OBSERVATIONS (contd)

5.5 Terminal Studies (contd)

Late Death - Separate embryonic/foetal and placental tissue visible.

Dead Foetus - A foetus that had died shortly before necropsy. These were included as late deaths for reporting purposes.

All implantations and viable foetuses were numbered according to their intrauterine position as follows:

<u>Left Horn</u>	<u>Cervix</u>	<u>Right Horn</u>
L1 L2 L3 L4 L5 L6 L7 L8		R1 R2 R3 R4 R5 R6 R7 R8
V1 V2 V3 V4 V5 V6 V7 V8		V9 V10 V11 V12 V13 V14 V15 V16

V = viable foetus

- iii) Foetal sex
- iv) External foetal appearance
- v) Foetal weight

The foetuses were killed by intraperitoneal injection of sodium pentobarbitone.

6. EVALUATION OF DATA

Data were processed to give litter mean values, group mean values and standard deviations.

- i) Absolute bodyweight change of females during gestation was calculated and presented relative to day 6 of gestation (day 1 of treatment).

6. EVALUATION OF DATA (contd)

ii) Percentage pre-implantation loss was calculated as:

$$\frac{\text{number of corpora lutea} - \text{number of implantations}}{\text{number of corpora lutea}} \times 100$$

percentage post-implantation loss was calculated as:

$$\frac{\text{number of implantations} - \text{number of live foetuses}}{\text{number of implantations}} \times 100$$

## 7. RESULTS

### 7.1 Mortality Data

There were no deaths.

### 7.2 Clinical Observations (Table 1, Appendix I)

At 100 mg/kg there were clinical signs of post dosing salivation and lethargy in 5/8 animals. Ptosis was also noted in one animal. At 50 mg/kg one animal showed transient signs of diarrhoea.

### 7.3 Bodyweight (Tables 2 and 3, Appendices II and III)

There were no treatment related effects on bodyweight gain during pregnancy.

### 7.4 Food Consumption (Table 4, Appendix IV)

At 100 mg/kg there was a slight reduction in food consumption over the period of day 6 to day 9 of gestation.

### 7.5 Terminal Studies

#### a) Adult Necropsy Data

There were no treatment related findings noted at necropsy.

The incidental findings recorded at necropsy were consistent with those normally expected in laboratory maintained rats.

#### b) Uterine/Implantation Data (Table 5)

The pregnancy rate was 8/8, 8/8, 8/8, 7/8 for 0, 10, 50 and 100 mg/kg respectively. There were no treatment related effects on uterine/implantation data.

#### c) Foetal Data (Tables 6 and 7, Appendices V and VI)

There were no treatment related foetal findings.

DISCUSSION

At 100 mg/kg there was a slight reduction in group mean food consumption over the period of day 6 to day 9 of gestation. There were also clinical signs of lethargy and post dosing salivation seen at this dose level. These were considered to be indicative of slight maternal toxicity. There were no treatment related effects at other dose levels.

There were no treatment related effects on pregnancy or foetuses at any dose level.

CONCLUSION

Treatment of pregnant females with IPPD at dose levels of up to 100 mg/kg, from day 6 to 15 of gestation resulted in slight maternal toxicity at 100 mg/kg only. There were no treatment related effects on pregnancy or foetuses at any dose level.

ARCHIVE

Unless instructed otherwise by the sponsor, all original data, specimens and a copy of the final report will be retained in the archives of Safepharm Laboratories for a period of ten years. After this period, the sponsor's instructions will be sought.

Specimens will be taken to include test material, any tissues, or foetal specimens derived from the test system for examination or analysis.

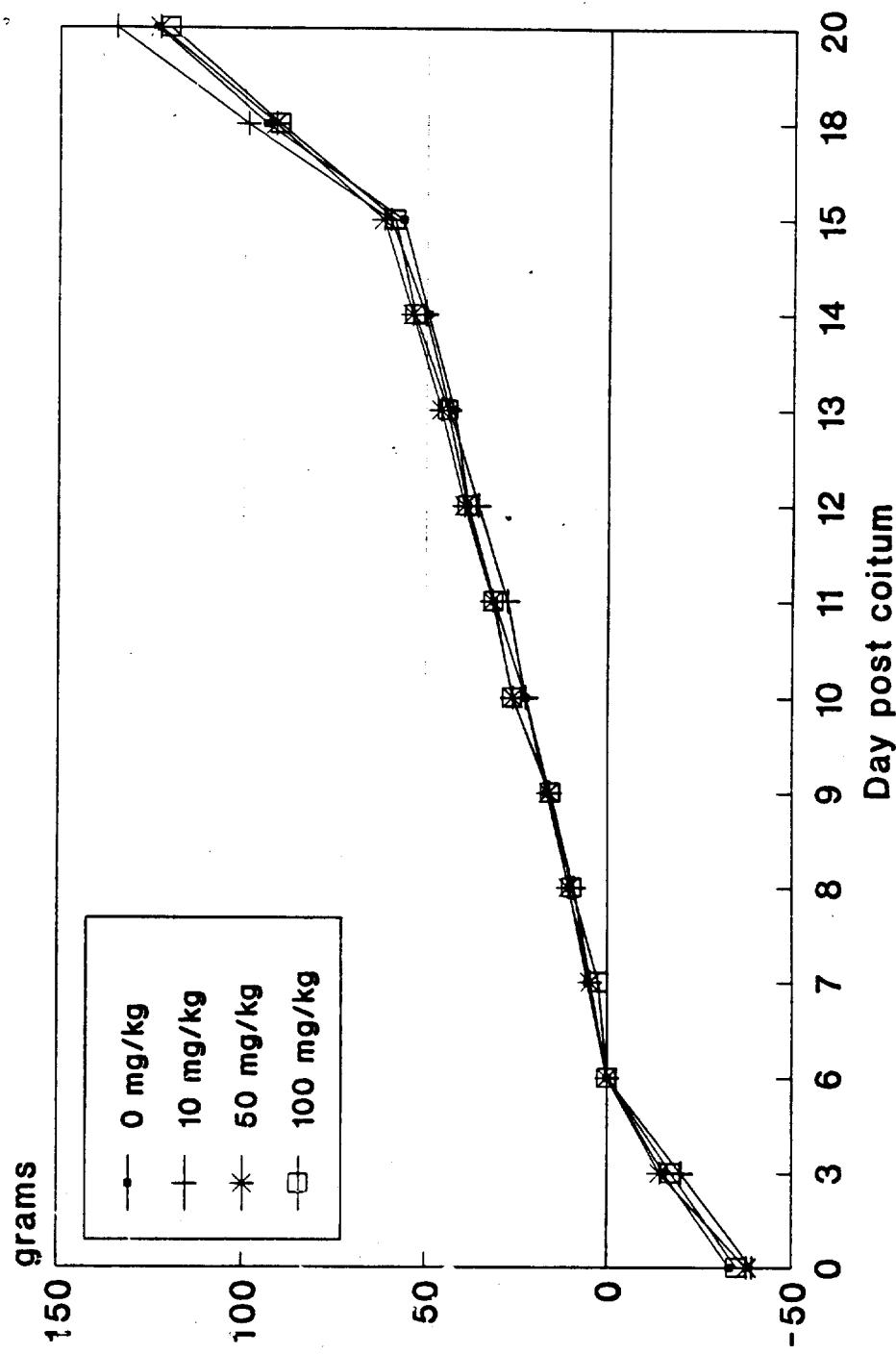
Primary data will be taken to include laboratory data sheets, computer print-outs, records, memoranda, file notes and photographs that are a result of the original observations and activities of the study and which are necessary for the reconstruction and evaluation of the report of the study.

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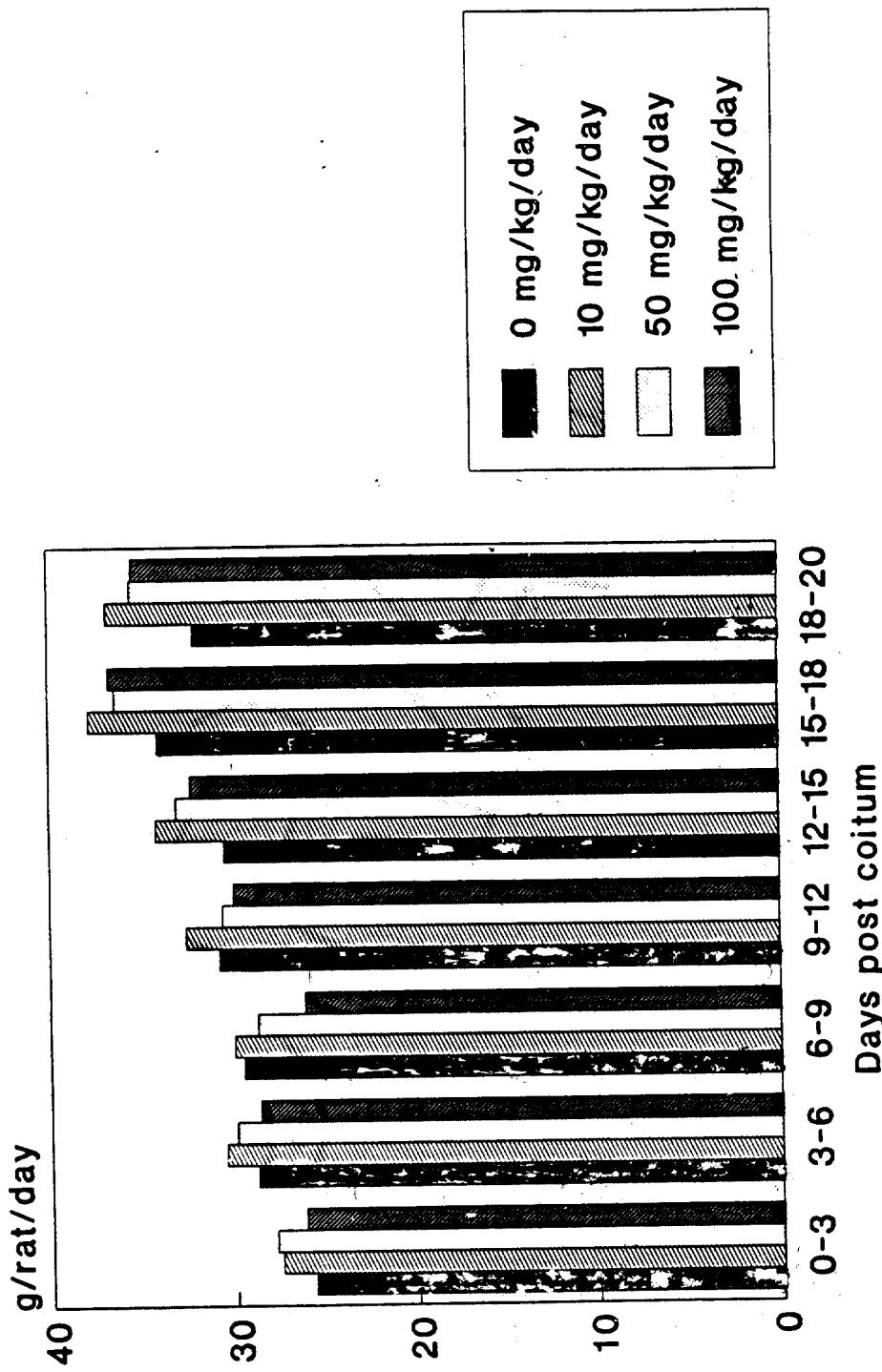
F I G U R E S

FIGURE I  
GROUP MEAN BODYWEIGHT CHANGE (g)  
OF PREGNANT FEMALES POST COITUM\*



\* • relative to day 6 post coitum

GROUP MEAN FOOD CONSUMPTION (g/rat/day)  
OF PREGNANT FEMALES POST COITUM





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T A B L E S

TABLE 1  
SUMMARY INCIDENCE OF DAILY CLINICAL OBSERVATIONS

Group	Dose Level mg/kg	Clinical Observations	Number of Animals Affected	Group Mean Day of	
				Observation First Recorded	Observation Last Recorded
1	0	NAD	0		
2	10	NAD	0		
3	50	Diarrhoea	1	9	12
4	100	Salivation 2 minutes after dosing Lethargy (P.D.) Ptosis (P.D.)	5 5 1	11 11 9	12 15 13

P.D. - Observation seen after dosing only

TABLE 2  
GROUP MEAN BODYWEIGHT (g) OF PREGNANT FEMALES POST COITUM

Group	Dose Level mg/kg	Day Post Coitum														
		0	3	6	7	8	9	10	11	12	13	14	15	18	20	
1	0	Mean	249	267	282	288	293	299	305	313	321	325	332	339	376	406
	S.D.	18.4	20.3	22.9	21.7	20.8	22.5	23.0	21.7	21.8	21.6	22.0	25.2	27.0	30.6	
	N	8	8	8	8	8	8	8	8	8	8	8	8	8	8	
2	10	Mean	248	268	288	293	297	304	310	315	323	332	338	348	387	423
	S.D.	12.1	11.4	15.9	17.3	17.0	19.4	17.7	17.3	19.2	20.4	19.8	20.5	25.1	31.1	
	N	8	8	8	8	8	8	8	8	8	8	8	8	8	8	
3	50	Mean	247	271	285	290	296	301	311	317	324	331	339	347	377	408
	S.D.	16.3	14.5	19.0	19.4	19.7	21.2	18.9	18.2	21.2	21.3	23.2	25.2	30.3	34.2	
	N	8	8	8	8	8	8	8	8	8	8	8	8	8	8	
4	100	Mean	247	265	283	285	292	298	309	314	321	327	336	342	373	403
	S.D.	15.1	14.2	12.1	15.4	14.5	18.1	18.4	18.6	14.5	19.3	17.8	17.6	14.1	14.5	
	N	7	7	7	7	7	7	7	7	7	7	7	7	7	7	

S.D. = standard deviation

N = number of animals

TABLE 3  
GROUP MEAN BODYWEIGHT CHANGE (g) OF PREGNANT FEMALES POST COITUM\*

Group	Dose Level mg/kg	Day Post Coitum														
		0	3	6	7	8	9	10	11	12	13	14	15	18	20	
1	0	Mean	-33.4	-15.5	5.4	10.4	16.6	22.4	31.1	38.4	42.4	49.5	56.5	93.9	123.9	
		S.D.	8.58	8.60	*	4.17	3.78	3.38	3.07	3.64	2.88	4.21	3.74	3.89	7.16	8.77
		N	8	8	8	8	8	8	8	8	8	8	8	8	8	
2	10	Mean	-39.5	-20.1	4.6	9.1	15.8	22.4	27.5	35.5	43.6	50.3	59.9	99.1	134.8	
		S.D.	7.13	5.30	*	2.26	1.81	5.28	4.07	4.57	4.84	5.66	5.68	6.31	12.15	19.32
		N	8	8	8	8	8	8	8	8	8	8	8	8	8	
3	50	Mean	-38.1	-14.5	4.6	10.5	15.9	25.9	31.6	39.3	45.9	53.8	61.8	91.4	123.1	
		S.D.	4.32	7.21	*	2.77	2.56	4.58	4.88	4.60	5.70	6.77	7.69	9.38	17.65	24.25
		N	8	8	8	8	8	8	8	8	8	8	8	8	8	
4	100	Mean	-35.4	-17.7	2.3	9.6	15.4	26.1	31.3	38.6	44.1	53.1	58.7	90.4	120.3	
		S.D.	6.45	5.91	*	3.95	3.36	7.44	7.22	8.86	6.55	9.21	9.72	8.18	4.39	9.11
		N	7	7	-	7	7	7	7	7	7	7	7	7	7	

S.D. = standard deviation

N = number of animals

\* = relative to day 6 post coitum

TABLE 4  
GROUP MEAN FOOD CONSUMPTION (g/RAT/DAY) OF PREGNANT FEMALES POST COITUM

Group	Dose Level mg/kg	Days Post Coitum					
		0-3	3-6	6-9	9-12	12-15	15-18
1 0	Mean	25.7	28.8	29.5	30.8	30.5	34.1
	S.D.	2.2	2.8	4.0	2.7	2.6	3.2
	N	8	8	8	8	8	8
2 10	Mean	27.5	30.5	30.0	32.6	34.2	37.8
	S.D.	2.2	3.0	2.2	3.5	3.3	5.1
	N	8	8	8	8	8	8
3 50	Mean	27.8	29.9	28.7	30.6	33.1	36.4
	S.D.	2.2	2.9	2.6	4.7	3.7	4.4
	N	8	8	8	8	8	8
4 100	Mean	26.2	28.6	26.1	30.1	32.3	36.7
	S.D.	2.3	2.4	3.2	1.8	3.8	2.1
	N	7	7	7	7	7	7

S.D. = standard deviation

N = number of animals

IPPO : PRELIMINARY ORAL GAVAGE TERATOLOGY STUDY IN THE RAT

TABLE 5 SUMMARY OF ADULT PERFORMANCE

	Dose Level mg/kg	0	10	50	100
Number of females in group	8	8	8	8	8
Number pregnant	8	8	8	7	
Number died/killed before day 20	0	0	0	0	0
Number not pregnant	0	0	0	0	1
Number with total litter loss	0	0	0	0	0

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TABLE 6  
GROUP MEAN LITTER DATA

Group	Dose Level (mg/kg)	Number of Animals	Number of Pregnant	Number of corpora lutea	Number of Live Foetuses	Male Foetuses	Embryonic/Foetal Deaths			Implantation Loss %		Total Litter Weight (g)	Mean Foetal Weight (g)
							Early	Late	Total	Pre	Post		
1	0	8	8	18.6	14.8	45.9	1.1	0.0	1.1	13.1	7.1	53.76	3.64
2	10	8	8	18.1	14.9	45.8	0.8	0.1	0.9	11.8	5.7	56.68	3.81
3	50	8	8	16.1	12.6	58.0	0.6	0.1	0.8	19.6	6.9	49.70	4.06
4	100	8	7	15.8	13.3	44.0	0.9	0.0	0.9	9.5	6.4	50.48	3.81

IPPD : PRELIMINARY ORAL GAVAGE TERATOLOGY STUDY IN THE RAT

TABLE 7 GROUP INCIDENCE OF FOETAL EXTERNAL FINDINGS

External Findings	Number of Foetuses Examined					
	Dose Level mg/kg					
	0	10	50	100		
118	119	101	93			
NF	NL	%*	NF	NL	%*	NF
2	2	1.7	1	1	0.8	1
Total Number Affected				1	1	1.0
a - small foetus	2	2	1.7	1	0.8	0
b - right hind limb malrotated	0	0	-	0	0	-

a - small foetus  
b - right hind limb malrotated

NOTE: A foetus may appear in more than one category

\* = group mean per litter

NF = number of foetuses in category

NL = number of litters in category

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A P P E N D I C E S

APPENDIX I                    INDIVIDUAL ADULT CLINICAL SIGNS AND NECROPSY FINDINGS

GROUP: 1                    DOSE LEVEL (mg/kg): 0

Dam Number	Status	Clinical Signs (Onset and Final Observation)		Necropsy Finding
		Days Post Coitum		
6	TK		NAD	Left kidney enlarged Right kidney and right adrenal missing

TK = terminal kill

NAD = no abnormalities detected

IPPD : PRELIMINARY ORAL GAVAGE TERATOLOGY STUDY IN THE RAT

INDIVIDUAL ADULT CLINICAL SIGNS AND NECROPSY FINDINGS

APPENDIX I

(contd)

GROUP: 3

DOSE LEVEL (mg/kg): 50

Dam Number	Status	Clinical Signs (Onset and Final Observation)		Necropsy Finding
		Days Post Coitum		
21	TK		Diarrhoea (9,12)	NAD
				NAD = no abnormalities detected

TK = terminal kill

**APPENDIX I**  
**(contd)**

**IPPD : PRELIMINARY ORAL GAVAGE TERATOLOGY STUDY IN THE RAT**  
**INDIVIDUAL ADULT CLINICAL SIGNS AND NECROPSY FINDINGS**

**GROUP: 4**

**DOSE LEVEL (mg/kg): 100**

<b>Dam Number</b>	<b>Status</b>	<b>Clinical Signs (Onset and Final Observation)</b>		<b>Necropsy Finding</b>
		<b>Days Post Coitum</b>	<b>Days Post dosing</b>	
25	TK	Salivation 2 minutes after dosing (11) Lethargy (post dosing)	(11-13,15)	NAD
26	TK	Salivation 2 minutes after dosing (12) Lethargy (post dosing)	(11-15)	NAD
27	TK	Salivation 2 minutes after dosing (10,11,14)		NAD
28	TK	Salivation 2 minutes after dosing (10,13,14) Lethargy (post dosing)	(11-15)	NAD
29	TK	Lethargy (post dosing)	(14,15)	NAD
30	TK	Salivation 2 minutes after dosing (11)		NAD
31	TK	Lethargy (post dosing) Ptosis (post dosing)	(9-15) (9,10,13)	NAD
32	TK			Increased renal pelvic cavitation of right kidney

**TK = terminal kill**

**NAD = no abnormalities detected**

IPPD : PRELIMINARY ORAL GAVAGE TERATOLOGY STUDY IN THE RAT

APPENDIX III

INDIVIDUAL BODYWEIGHTS (g) OF FEMALES POST COITUM

GROUP: 1

DOSE LEVEL (mg/kg): 0

Animal Number	Day Post Coitum													
	0	3	6	7	8	9	10	11	12	13	14	15	18	20
1	259	278	302	313	315	326	333	340	347	352	366	401	434	
2	218	232	249	252	260	265	270	280	293	294	296	299	336	363
3	250	262	284	289	292	301	304	312	320	332	336	340	374	407
4	253	269	292	295	301	304	311	322	327	328	337	346	378	417
5	275	298	318	324	325	338	343	349	358	355	363	375	416	458
6	226	246	255	268	274	277	283	293	294	296	306	312	343	378
7	258	275	275	285	283	290	297	309	314	320	331	332	372	389
8	252	274	283	285	293	301	303	309	319	325	333	340	389	403

IPPD : PRELIMINARY ORAL GAVAGE TERATOLOGY STUDY IN THE RAT

APPENDIX III  
(contd)

GROUP: 2

Animal Number	Day Post Coitum										DOSE LEVEL (mg/kg): 10			
	0	3	6	7	8	9	10	11	12	13	14	15	18	20
9	252	272	300	305	310	314	324	326	340	342	348	354	390	411
10	240	267	286	294	294	299	307	311	319	324	331	342	377	409
11	242	260	277	281	287	290	296	308	311	317	326	334	369	416
12	235	250	263	265	269	270	280	287	293	299	305	314	344	373
13	259	276	299	303	307	315	319	319	329	351	353	365	407	453
14	264	273	298	301	307	316	320	329	335	346	348	362	405	457
15	234	258	272	275	282	293	301	301	308	316	326	334	380	402
16	261	286	308	316	320	332	335	342	352	357	368	377	424	460

IPPD : PRELIMINARY ORAL GAVAGE TERATOLOGY STUDY IN THE RAT

A P P E N D I X    I I  
(contd)

INDIVIDUAL BODYWEIGHTS (g) OF FEMALES POST COITUM

GROUP: 3

DOSE LEVEL (mg/kg): 50

Animal Number	Day Post Coitum													
	0	3	6	7	8	9	10	11	12	13	14	15	18	20
17	251	274	291	294	300	306	322	329	341	343	352	360	390	424
18	246	267	285	286	293	296	303	309	318	318	323	328	347	370
19	261	284	296	303	310	311	318	322	332	343	355	363	402	452
20	240	256	276	277	283	290	301	309	311	317	330	334	365	406
21	260	276	296	304	309	315	326	329	335	345	355	366	373	390
22	240	267	281	285	290	292	303	314	317	323	330	342	369	401
23	214	248	246	253	258	263	277	281	286	296	297	302	336	366
24	264	293	310	316	322	335	338	341	355	363	369	380	430	457

IPPD : PRELIMINARY ORAL GAVAGE TERATOLOGY STUDY IN THE RAT

APPENDIX II  
(contd)

GROUP: 4

DOSE LEVEL (mg/kg): 100

Animal Number	Day Post Coitum													
	0	3	6	7	8	9	10	11	12	13	14	15	18	20
25	257	270	290	290	300	303	322	324	329	339	344	353	381	405
26	220	239	258	254	263	264	274	282	299	293	309	311	347	379
27	233	256	280	282	291	293	302	310	316	322	333	337	363	401
28	250	261	283	285	292	299	311	316	323	332	340	348	380	420
29	256	275	295	304	310	325	333	344	344	352	364	363	387	420
31	256	276	284	288	295	302	308	308	311	314	320	328	372	393
32	260	279	290	293	296	302	313	315	328	337	342	351	383	404
30 (not pregnant)	267	290	316	320	322	332	339	348	349	355	350	343	337	339

IPPD : PRELIMINARY ORAL GAVAGE TERATOLOGY STUDY IN THE RAT

APPENDIX III

INDIVIDUAL BODYWEIGHT CHANGE OF FEMALES POST COITUM\*

GROUP: 1

Animal Number	Day Post Coitum									
	0	3	6	7	8	9	10	11	12	13
1	-43	-24	*	1	11	13	24	31	38	45
2	-31	-17	*	3	11	16	21	31	44	45
3	-34	-22	*	5	8	17	20	28	36	48
4	-39	-23	*	3	9	12	19	30	35	36
5	-43	-20	*	6	7	20	25	31	40	37
6	-29	-9	*	13	19	22	28	38	39	41
7	-17	0	*	10	8	15	22	34	39	45
8	-31	-9	*	2	10	18	20	26	36	42
										50
										57
										106
										120

\* = relative to day 6 post coitum

IPPO : PRELIMINARY ORAL GAVAGE TERATOLOGY STUDY IN THE RAT

APPENDIX III  
(contd)

GROUP: 2

DOSE LEVEL (mg/kg): 10

Animal Number	Day Post Coitum													
	0	3	6	7	8	9	10	11	12	13	14	15	18	20
9	-48	-28	*	5	10	14	24	26	40	42	48	54	90	111
10	-46	-19	*	8	8	13	21	25	33	38	45	56	91	123
11	-35	-17	*	4	10	13	19	31	34	40	49	57	92	139
12	-28	-13	*	2	6	7	17	24	30	36	42	51	81	110
13	-40	-23	*	4	8	16	20	20	30	52	54	66	108	154
14	-34	-25	*	3	9	18	22	31	37	48	50	64	107	159
15	-38	-14	*	3	10	21	29	36	44	54	62	108	130	
16	-47	-22	*	8	12	24	27	34	44	49	60	69	116	152

\*-- relative to day 6 post coitum

IPPO : PRELIMINARY ORAL GAVAGE TERATOLOGY STUDY IN THE RAT

APPENDIX III  
(contd)

GROUP: 3

DOSE LEVEL (mg/kg): 50

INDIVIDUAL BODYWEIGHT CHANGE OF FEMALES POST COITUM\*

Animal Number	Day Post Coitum													
	0	3	6	7	8	9	10	11	12	13	14	15	18	20
17	-40	-17	*	3	9	15	31	38	50	52	61	69	99	133
18	-39	-18	*	1	8	11	18	24	33	33	38	43	62	85
19	-35	-12	*	7	14	15	22	26	36	47	59	67	106	156
20	-36	-20	*	1	7	14	25	33	35	41	54	58	89	130
21	-36	-20	*	8	13	19	30	33	39	49	59	70	77	94
22	-41	-14	*	4	9	11	22	33	36	42	49	61	88	127
23	-32	2	*	7	12	17	31	35	40	50	51	56	90	120
24	-46	-17	*	6	12	25	28	31	45	53	59	70	120	147

\* = relative to day 6 post coitum

APPENDIX III  
(contd)  
INDIVIDUAL BODYWEIGHT CHANGE OF FEMALES POST COITUM\*

GROUP: 4	Animal Number	Day Post Coitum										DOSE LEVEL (mg/kg): 100			
		0	3	6	7	8	9	10	11	12	13	14	15	18	20
25	-33	-20	*	0	10	13	32	34	39	49	54	63	91	115	
26	-38	-19	*	-4	5	6	16	24	41	35	51	53	89	121	
27	-47	-24	*	2	11	13	22	30	36	42	53	57	83	121	
28	-33	-22	*	2	9	16	28	33	40	49	57	65	97	137	
29	-39	-20	*	9	15	30	38	49	49	57	69	68	92	125	
31	-28	-8	*	4	11	18	24	24	27	30	36	44	88	109	
32	-30	-11	*	3	6	12	23	25	38	47	52	61	93	114	
30 (not pregnant)	-49	-26	*	4	6	16	23	32	33	39	34	27	21	23	

**APPENDIX IV****IPPD : PRELIMINARY ORAL GAVAGE TERATOLOGY STUDY IN THE RAT  
INDIVIDUAL FOOD CONSUMPTION (g/RAT/DAY) OF FEMALES POST COITUM****GROUP: 1****DOSE LEVEL (mg/kg): 0**

Animal Number	Days Post Coitum						
	0-3	3-6	6-9	9-12	12-15	15-18	18-20
1	26.3	32.0	31.7	35.0	31.7	34.0	35.5
2	22.0	24.7	26.3	28.3	27.0	30.0	28.0
3	23.7	28.3	30.3	32.7	31.0	34.7	34.5
4	27.0	31.3	30.7	31.3	30.3	34.3	33.0
5	29.0	31.7	26.0	32.0	30.7	39.3	33.5
6	26.3	28.0	37.0	28.0	28.0	31.0	30.0
7	24.3	25.3	24.3	27.3	29.7	31.7	29.0
8	26.7	29.0	30.0	31.7	35.7	37.7	33.5

**APPENDIX IV**  
**(contd)**

**GROUP: 2**

**IPPO : PRELIMINARY ORAL GAVAGE TERATOLOGY STUDY IN THE RAT**  
**INDIVIDUAL FOOD CONSUMPTION (g/RAT/DAY) OF FEMALES POST COITUM**

Animal Number	Days Post Coitum					DOSE LEVEL (mg/kg): 10
	0-3	3-6	6-9	9-12	12-15	
9	26.3	30.0	30.3	31.0	31.3	34.7
10	27.0	30.0	30.0	31.3	31.7	32.0
11	25.0	29.3	29.7	29.0	32.3	35.3
12	27.0	28.3	27.3	30.7	31.0	33.3
13	30.0	37.0	30.0	38.3	38.3	45.7
14	26.7	30.0	30.3	34.3	35.7	42.0
15	26.3	27.3	27.7	29.3	33.7	36.0
16	31.7	32.3	34.7	37.0	39.7	43.0

APPENDIX IV  
(contd)  
GROUP: 3  
INDIVIDUAL FOOD CONSUMPTION (g/RAT/DAY) OF FEMALES POST COITUM

Animal Number	Days Post Coitum					DOSE LEVEL (mg/kg): 50
	0-3	3-6	6-9	9-12	12-15	
17	27.0	29.3	27.7	35.3	34.3	34.7
18	29.3	29.7	28.3	30.3	30.0	32.0
19	28.3	31.7	29.0	35.7	35.0	42.0
20	25.3	27.7	25.3	30.3	31.0	34.0
21	28.7	30.3	32.0	22.3	35.0	38.0
22	27.3	31.3	30.0	33.7	36.7	39.0
23	25.0	24.7	25.3	25.3	26.3	30.0
24	31.7	34.3	31.7	32.0	36.7	41.7

IPPD : PRELIMINARY ORAL GAVAGE TERATOLOGY STUDY IN THE RAT

APPENDIX IV  
(contd)

GROUP: 4

DOSE LEVEL (mg/kg): 100

Animal Number	Days Post Coitum				
	0-3	3-6	6-9	9-12	12-15
25	25.0	28.0	26.7	32.0	28.7
26	23.0	26.0	22.3	28.7	30.3
27	26.0	29.3	25.7	29.3	29.3
28	27.3	30.3	27.7	31.7	32.0
29	30.3	32.7	32.0	32.0	40.0
31	25.3	28.0	25.3	28.0	32.7
32	26.7	26.0	23.0	28.7	33.3
30 (not pregnant)	32.3	33.7	32.3	34.3	30.3

APPENDIX V

INDIVIDUAL CAESARIAN NECROPSY FINDINGS

KEY TO FOETAL EXTERNAL FINDINGS

a - small foetus

b - right hind limb malrotated

IPPD : PRELIMINARY ORAL GAVAGE TERATOLOGY STUDY IN THE RAT

APPENDIX V  
INDIVIDUAL LITTER DATA

GROUP: 1

DOSE LEVEL (mg/kg): 0

Animal Number	Total Number of Corpora Lutea			Number of Live Implants			Number of Dead Implants			Implantation Loss %			Total Litter Weight (g)	Mean Foetal Weight (g)	
										Pre		Post			
	Male	Female	Total	Foetuses	Male	Total	Early	Late	Total	Pre	Post	Pre	Post		
1	20	7	8	15	46.7	0	0	0	0	25.0	0	51.8	3.45		
2	16	8	6	14	57.1	2	0	2	0	12.5	0	50.5	3.60		
3	22	8	6	14	57.1	2	0	2	27.3	12.5	52.0	3.71			
4	23	6	9	15	40.0	1	0	1	30.4	6.3	52.5	3.50			
5	18	8	9	17	47.1	0	0	0	5.6	0	66.6	3.92			
6	16	5	10	15	33.3	1	0	1	0	6.3	57.8	3.85			
7	16	3	11	14	21.4	2	0	2	0	12.5	49.3	3.52			
8	18	9	5	14	64.3	1	0	1	16.7	6.7	49.6	3.55			

IPPD : PRELIMINARY ORAL GAVAGE TERATOLOGY STUDY IN THE RAT

A P P E N D I X V  
(contd)  
INDIVIDUAL LITTER DATA

GROUP: 2                          DOSE LEVEL (mg/kg): 10

Animal Number	Total Number of Corpora Lutea	Number of Live Implants			Number of Dead Implants			Implantation Loss %		Total Litter Weight (g)	Mean Foetal Weight (g)		
								Pre	Post				
		Hale	Female	Total	Hale	Female	Total						
9	17	3	8	11	27.3	1	0	1	29.4	8.3	43.2		
10	14	8	5	13	61.5	1	0	1	0	7.1	49.1		
11	19	8	9	17	47.1	0	1	1	5.3	5.6	65.3		
12	16	7	8	15	46.7	1	0	1	0	6.3	54.6		
13	20	9	7	16	56.3	1	0	1	15.0	5.9	64.3		
14	17	7	10	17	41.2	0	0	0	0	0	68.8		
15	18	8	7	15	53.3	1	0	1	11.1	6.3	53.7		
16	24	5	10	15	33.3	1	0	1	33.3	6.3	54.5		

IPPD : PRELIMINARY ORAL CAVAGE TERATOLOGY STUDY IN THE RAT

## APPENDIX V (cont'd.)

### INDIVIDUAL LITTER DATA

GROUP: 3

DOSSE LEVEL (mg/kg) : 50

Animal Number	Total Number of Corpora Lutea	Number of Live Implants			Male Foetuses	Number of Dead Implants			Implantation Loss %			Total Litter Weight (g)	Mean Foetal Weight (g)			
				Male		Early	Late	Total	Pre	Post						
17	18	7	7	14	50.0	1	0	1	16.7	6.7	55.7	3.98				
18	15	3	2	5	60.0	2	0	2	53.3	28.6	20.6	4.11				
19	21	6	10	16	37.5	0	0	0	23.8	0	64.6	4.04				
20	19	7	11	18	38.9	0	0	0	5.3	0	71.4	3.97				
21	5	3	0	3	100	0	0	0	40.0	0	15.2	5.05				
22	16	6	6	12	50.0	2	1	3	6.3	20.0	44.7	3.73				
23	18	12	4	16	75.0	0	0	0	11.1	0	56.2	3.51				
24	17	9	8	17	52.9	0	0	0	0	0	69.2	4.07				

PRELIMINARY ORAL GAVAGE TERATOLOGY STUDY IN THE RAT

**APPENDIX V  
(contd.)**

INDIVIDUAL LITTE

4001P.

DOSER LEVEL (mg/kg) : 100

Animal Number	Total Number of Corpora Lutea	Number of Live Implants			Male Foetuses	Female Foetuses	Total Foetuses	Number of Dead Implants			Implantation Loss %		Total Litter Weight (g)	Mean Foetal Height (g)	
								Early	Late	Total	Pre	Post			
		Male	Female	Total											
25	13	4	6	10	40.0		3	0	3	0	23.1		41.3	4.13	
26	17	5	10	15	33.3		0	0	0	11.8	0	59.9		3.97	
27	15	9	5	14	64.3		1	0	1	0	6.7		53.1		3.79
28	21	5	10	15	33.3		0	0	0	28.6		55.8		3.72	
29	15	3	10	13	23.1		1	0	1	6.7		7.1		50.4	3.87
31	16	9	5	14	64.3		0	0	0	12.5		0		51.2	3.65
32	14	6	6	12	50.0		1	0	1	7.1		7.7		41.7	3.48

IPPD : PRELIMINARY ORAL GAVAGE TERATOLOGY STUDY IN THE RAT

A P P E N D I X VI

INDIVIDUAL CAESARIAN NECROPSY FINDINGS

GROUP: 1

DOSE LEVEL (mg/kg): 0

Dam Number	Parameter	Implantation Number												Right Horn of Uterus		
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1	Implant Type*	V1	V2	V3	V4	V5	V6	V7	V8	V9	C	V10	V11	V12	V13	V15
	FWT (g)	3.94	3.46	3.65	1.81	3.56	3.69	3.74	2.70	3.60		4.21	2.54	3.63	4.04	4.01
	Sex	H	H	F	F	H	H	H	F	H		F	F	F	F	F
	PUT (g)															
2	Implant Type*	V1	V2	V3	V4	V5	V6	V7	V8	V9	C	V10	V11	ED	V12	V14
	FWT (g)	3.42	3.54	3.34	3.66	3.82	3.50	3.41	3.56	3.65	3.57	3.92		3.82		3.54
	Sex	F	F	F	H	H	H	F	F	H				F	H	H
	PUT (g)															
3	Implant Type*	V1	V2	C	V3	ED	V4	V5	V6	V7		V8	V9	V10	V11	V14
	FWT (g)	3.75	3.54	4.34	H	H	H	F	H	3.77	4.00	3.74	3.57	3.47	3.73	3.32
	Sex	F	F	H					H			F	F	H	F	F
	PUT (g)															
4	Implant Type*	V1	V2	V3	V4	V5	V6	V7	V8	V9		V10	V11	V12	V13	V15
	FWT (g)	3.48	2.94	3.77	3.40	3.40	3.72	3.69	3.16	3.52	3.46	3.77	3.69	3.33	3.86	3.32
	Sex	H	F	F	H	H	H	F	F	F				F	H	F
	PUT (g)															
5	Implant Type*	V1	V2	V3	V4	V5	V6	V7	V8	V9	C	V10	V11	V12	V13	V16
	FWT (g)	3.72	3.81	3.98	4.13	3.58	4.18	4.05	3.89	4.00	3.78	4.04		3.87	4.11	3.78
	Sex	F	F	F	H	F	H	H	H	F				H	H	F
	PUT (g)															

H = male  
ED = early death

F = female  
FWT = foetal weight

C = cervix  
PUT = placental weight

\* = viable foetuses are identified by assigned foetal number

IPPD : PRELIMINARY ORAL GAVAGE TERATOLOGY STUDY IN THE RAT

APPENDIX VI (contd)

INDIVIDUAL CAESARIAN NECROPSY FINDINGS

GROUP: 1 (contd)

DOSE LEVEL (mg/kg): 0

Dam Number	Parameter	Implantation Number														Right Horn of Uterus			
		Left Horn of Uterus	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	
5 (contd)	Implant Type <sup>*</sup>	V17																	
	FWT (g)	3.88																	
6	Sex	M																	
	PWT (g)	F																	
	Findings																		
7	Implant Type <sup>*</sup>	V1	V2	V3	V4	V5	V6	ED	C	V7	V8	ED	V9	V10	V11	V12	V13	V14	
	FWT (g)	3.69	3.63	3.62	3.75	3.78	3.94			3.36	3.52		3.80	3.39	3.57	3.81	3.18	2.28	
	Sex	F	F	F	F	F	F			F	F		H	F	F	H	F	F	
	PWT (g)																		
	Findings																		
8	Implant Type <sup>*</sup>	V1	V2	V3	V4	V5	C	V6	V7	V8	ED	V9	V10	V11	V12	V13	V14		
	FWT (g)	3.57	3.78	3.49	3.80	3.44		3.43	3.58	3.87		3.09	3.61	3.55	3.76	3.41	3.25		
	Sex	H	H	H	H	F		F	H	H		H	F	H	F	H			
	PWT (g)																		
	Findings																		

M = male  
ED = early death

F = female  
FWT = foetal weight

\* = viable foetuses are identified by assigned foetal number

C = cervix

PWT = placental weight

IPPD : PRELIMINARY ORAL GAVAGE TERATOLOGY STUDY IN THE RAT

APPENDIX V I (contd)

INDIVIDUAL CAESARIAN NECROPSY FINDINGS

GROUP: 2

DOSE LEVEL (mg/kg): 10

Dam Number	Parameter	Implantation Number												
		1	2	3	4	5	6	7	8	9	10	11	12	
9	Implant Type*	V1	V2	V3	V4	V5	V6	ED	C	V7	V8	V9	V10	V11
	FWT (g)	3.74	3.95	3.78	4.02	4.22	3.91			4.23	4.00	3.86	3.92	3.59
	Sex	F	F	H	H	F	F			F	F	F	F	H
	PWT (g)													
	Findings													
10	Implant Type*	V1	V2	V3	C	V4	V5	V6	V7	V8	V9	V10	V11	ED
	FWT (g)	3.90	3.64	3.91	3.84	3.56	3.64	3.76	3.78	3.67	4.07	3.61	3.90	3.77
	Sex	H	H	H	H	F	F	H	F	F	H	F	H	
	PWT (g)													
	Findings													
11	Implant Type*	V1	V2	V3	V4	V5	V6	V7	C	V8	V9	V10	L0	V12
	FWT (g)	3.75	4.05	4.07	3.76	3.84	3.49	3.88	3.85	4.20	3.56	3.99	3.84	V13
	Sex	F	H	H	H	F	F	H	H	F	F	F	F	
	PWT (g)													
	Findings													
11 (contd)	Implant Type*	V16	V17											V15
	FWT (g)	3.60	3.65											
	Sex	F	N											
	PWT (g)													
	Findings													
12	Implant Type*	V1	V2	V3	V4	V5	V6	V7	C	V8	V9	V10	V11	V12
	FWT (g)	3.52	3.54	3.90	4.06	3.59	3.73	3.86	3.63	3.46	3.42	3.71	3.42	V13
	Sex	H	F	H	H	F	F	F	H	F	F	F	H	
	PWT (g)													
	Findings													

M = male  
ED = early death

F = female  
FWT = foetal weight

C = cervix  
PWT = placental weight

LD = late death  
† = viable foetuses are identified by assigned foetal number

LD = late death

† = viable foetuses are identified by assigned foetal number

## IPPD : PRELIMINARY ORAL Gavage TERATOLOGY STUDY IN THE RAT

## APPENDIX V I (contd)

## INDIVIDUAL CAESARIAN NECROPSY FINDINGS

GROUP: 2 (contd)

DOSE LEVEL (mg/kg): 10

Dam Number	Parerector		Implantation Number															
			Left Horn of Uterus				Right Horn of Uterus											
			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
13	Implant Type*	V1 FWT (g) Sex PWT (g) Findings	3.86 3.61 F	V2 3.94 F	V3 4.21 N	V4 3.79 F	V5 3.88 N	V6 3.97 N	V7 4.33 N	V8 3.74 F	V9 4.30 F	V10 C 4.21 N	V11 4.29 N	V12 4.21 N	V13 4.28 N	V14 4.28 N	V15 4.14 N	
13 (contd)	Implant Type*	V16 FWT (g) Sex PWT (g) Findings	3.49 F															
14	Implant Type*	V1 FWT (g) Sex PWT (g) Findings	3.96 4.30 N	V2 3.92 F	V3 4.03 F	V4 4.57 N	V5 4.67 N	V6 3.66 F	V7 4.16 N	V8 3.68 F	V9 C 3.70 F	V10 3.98 F	V11 3.70 F	V12 3.84 F	V13 3.84 N	V14 3.85 N	V15 3.94 N	V16 4.06 F
14 (contd)	Implant Type*	V17 FWT (g) Sex PWT (g) Findings	3.99 F															
15	Implant Type*	V1 FWT (g) Sex PWT (g) Findings	3.63 3.46 N	V2 3.41 F	V3 3.57 N	V4 3.75 N	V5 3.57 N	V6 C 3.74 N	V7 3.42 F	V8 3.69 F	V9 3.37 F	V10 4.21 F	V11 3.60 F	V12 3.68 F	V13 3.60 N	V14 3.68 N	V15 3.85 N	ED 2.55
16	Implant Type*	V1 FWT (g) Sex PWT (g) Findings	3.68 3.58 N	V2 3.58 F	V3 3.81 N	V4 3.58 N	V5 3.81 N	V6 3.79 N	V7 3.43 F	V8 3.79 F	V9 3.20 F	V10 3.60 F	V11 3.67 F	V12 3.87 F	V13 3.90 N	V14 3.90 N	V15 3.55 F	ED 3.44

M = male  
ED = early deathF = female  
FWT = foetal weightC = cervix  
PWT = placental weight

\* = viable foetuses are identified by assigned foetal number

APPENDIX VI (contd)

INDIVIDUAL CAESARIAN NECROPSY FINDINGS

GROUP: 3

DOSE LEVEL (mg/kg): 50

Dam Number	Parameter	Implantation Number										Right Horn of Uterus				
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
17	Implant Type*	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	
	FWT (g)	4.34	3.95	4.61	3.62	3.69	4.33	ED	C	4.07	4.38	4.10	4.18	3.41	3.96	3.51
	Sex	M	M	M	F	F	H	F	H	F	H	F	H	H	F	
	PWT (g)															
	Findings															
13	Implant Type*	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15
	FWT (g)	4.16	4.37	4.42	3.77	ED	ED	V5								
	Sex	M	M	M	F											
	PWT (g)															
	Findings															
19	Implant Type*	V1	V2	V3	V4	V5	V6	C	V7	V8	V9	V10	V11	V12	V13	V16
	FWT (g)	4.22	3.79	4.04	4.15	4.25	4.00	4.17	4.18	4.10	3.97	3.89	3.74	4.09	4.07	3.92
	Sex	M	F	M	M	M	F	F	H	F	F	F	F	H	F	
	PWT (g)															
	Findings															
20	Implant Type*	V1	V2	V3	V4	V5	V6	V7	C	V8	V9	V10	V11	V12	V13	V16
	FWT (g)	3.98	4.54	3.94	4.18	4.31	3.91	4.19	4.21	3.81	3.96	3.65	4.04	3.88	4.08	4.01
	Sex	F	M	F	M	M	F	H	F	F	H	F	F	N	N	3.46
	PWT (g)															
	Findings															
20	Implant Type*	V17	V18													
(contd)	FWT (g)	3.34	3.89													
	Sex															
	PWT (g)															
	Findings															

M = male  
ED = early death

F = female  
FWT = foetal weight

C = cervix  
PWT = placental weight

\* = viable foetuses are identified by assigned foetal number

IPPD : PRELIMINARY ORAL GAVAGE TERATOLOGY STUDY IN THE RAT

A P P E N D I X V I (contd)

INDIVIDUAL CAESARIAN NECROPSY FINDINGS

GROUP: 3 (contd)

Dam Number	Parameter	Implantation Number												Right Horn of Uterus			
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
21	Implant Type*	V1	V2	V3													
	FWT (g)	4.92	5.19	5.04													
	Sex	M	M	M													
	PUT (g)																
	Findings																
22	Implant Type*	V1	V2	ED	V3	V4	V5	V6	V7	C	LD	V8	V9	V10	ED	V11	V12
	FWT (g)	3.76	3.30		3.72	3.84	3.96	3.72	3.63			3.61	3.71	3.75		3.73	4.01
	Sex	M	F		M	M	M	M	F			F	F	F			
	PUT (g)																
	Findings																
23	Implant Type*	V1	V2	V3	C	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15
	FWT (g)	3.34	3.24	3.78		3.79	3.50	3.50	3.64	3.70	4.01	3.66	3.42	3.13	3.44	3.27	V16
	Sex	M	F	M		M	M	M	M	M	H	H	F	F	F	F	3.50
	PUT (g)																
	Findings																
24	Implant Type*	V1	V2	V3		V4	V5	V6	V7	V8	C	V9	V10	V11	V12	V13	V16
	FWT (g)	3.90	4.01	4.23		3.86	4.30	4.24	4.14	4.35		3.90	4.44	4.28	4.47	4.32	4.00
	Sex	F	M	M		F	M	M	M	M		F	H	H	F	F	
(contd)	PUT (g)																
	Findings																
24	Implant Type*	V17															
	FWT (g)		4.11														
	Sex																
	PUT (g)																
	Findings																

M = male  
ED = early death

F = female  
FWT = foetal weight

C = cervix  
PUT = placental weight

LD = late death  
\* = viable foetuses are identified by assigned foetal number

IPPD : PRELIMINARY ORAL GAVAGE TERATOLOGY STUDY IN THE RAT

A P P E N D I X V I (contd)

INDIVIDUAL CAESARIAN NECROPSY FINDINGS

GROUP: 4

Dam Number	Parameter	Implantation Number															
		Left Horn of Uterus			Right Horn of Uterus												
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
25	Implant Type <sup>*</sup>	V1	V2	V3	V4	V5	C	ED	ED	C	ED	V6	V7	V8	V9	V10	
	FWT (g)	4.03	4.22	3.86	4.51	3.83						4.04	4.12	4.01	4.32	4.35	
	Sex	H	F	H	H	F						F	F	H	H		
	PWT (g)																
	Findings																
26	Implant Type <sup>*</sup>	V1	V2	V3	V4	V5	C	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15
	FWT (g)	4.11	4.08	4.21	4.19	4.17	4.02	3.89	4.11	3.84	3.80	3.90	4.00	3.83	4.15	3.61	
	Sex	H	F	H	F	F		H	F	F	F	F	H	F	H	F	
	PWT (g)																
	Findings																
27	Implant Type <sup>*</sup>	V1	V2	V3	V4	V5	V6	V7	V8	C	V9	V10	V11	V12	V13	V14	V15
	FWT (g)	3.89	3.89	4.09	3.59	4.01	3.98	4.00	3.92	2.98	4.06	3.35	3.77	3.88	3.68		
	Sex	H	F	H	F	H	F	F	H	H	H	F	H	H	H		
	PWT (g)																
	Findings																
28	Implant Type <sup>*</sup>	V1	V2	V3	V4	V5	V6	V7	C	V8	V9	V10	V11	V12	V13	V14	V15
	FWT (g)	3.46	3.90	3.77	4.04	3.87	3.89	4.12	3.81	3.52	3.70	3.69	4.27	3.63	3.69	2.47	
	Sex	F	F	H	H	F	F	H	F	H	F	F	H	F	F	F	
	PWT (g)																
	Findings																

H = male  
ED = early death

F = female  
FWT = foetal weight

C = cervix  
PWT = placental weight

\* = viable foetuses are identified by assigned foetal number

APPENDIX V I (contd)

INDIVIDUAL CAESARIAN NECROPSY FINDINGS

GROUP: 4 (contd) DOSE LEVEL (mg/kg): 100

Dam Number	Parameter	Implantation Number												Right Horn of Uterus			
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
29	Implant Type*	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	ED	V11	V12	V13	V14	
	FWT (g)	4.07	6.13	3.77	4.23	6.08	3.95	3.71	3.89	3.76	3.83	F	N	3.81	3.65	3.48	
	Sex	F	F	F	H	H	F	F	F	F	F		H	F	F		
	PWT (g)																
31	Implant Type*	V1	V2	V3	V4	V5	V6	V7	V8	C	V9	V10	V11	V12	V13	V14	
	FWT (g)	3.38	3.77	3.27	3.63	3.56	3.71	3.65	3.46	3.68	3.74	3.95	3.96	3.83	3.57		
	Sex	F	H	H	F	H	H	N	F	F	F	H	H	H	H		
	PWT (g)																
32	Implant Type*	V1	V2	V3	ED	V4	V5	C	V6	V7	V8	V9	V10	V11	V12	V13	
	FWT (g)	2.92	3.62	3.46		3.32	3.39	3.85	3.58	3.41	3.41	3.59	3.58	3.67	3.32		
	Sex	F	H	H		F	F	H	H	F	H	H	F	H	F		
	PWT (g)																

M = male  
ED = early death

F = female  
FWT = foetal weight

C = cervix  
PWT = placental weight

\* = viable foetuses are identified by assigned foetal number

APPENDIX VII

STUDY TIME PLAN

	<u>Date</u>
Study Directors Approval	21/12/92
Sponsors Approval	15/01/93
Animals Arrived	02/03/93
Start of Mating Period	16/03/93
Start of Dosing	22/03/93
Necropsy Start	05/04/93
Study Completed	08/04/93



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY  
WASHINGTON, D.C. 20460

Ronald D. Hogue, Ph.D.  
Manager, Product Safety  
Monsanto Chemical Company  
800 N. Lindbergh Boulevard  
St. Louis, Missouri 63167

OFFICE OF  
PREVENTION, PESTICIDES AND  
TOXIC SUBSTANCES

DEC 08 1994

EPA acknowledges the receipt of information submitted by your organization under Section 8(e) of the Toxic Substances Control Act (TSCA). For your reference, copies of the first page(s) of your submission(s) are enclosed and display the TSCA §8(e) Document Control Number (e.g., 8EHQ-00-0000) assigned by EPA to your submission(s). Please cite the assigned 8(e) number when submitting follow-up or supplemental information and refer to the reverse side of this page for "EPA Information Requests".

All TSCA 8(e) submissions are placed in the public files unless confidentiality is claimed according to the procedures outlined in Part X of EPA's TSCA §8(e) policy statement (43 FR 11110, March 16, 1978). Confidential submissions received pursuant to the TSCA §8(e) Compliance Audit Program (CAP) should already contain information supporting confidentiality claims. This information is required and should be submitted if not done so previously. To substantiate claims, submit responses to the questions in the enclosure "Support Information for Confidentiality Claims". This same enclosure is used to support confidentiality claims for non-CAP submissions.

Please address any further correspondence with the Agency related to this TSCA 8(e) submission to:

Document Processing Center (7407)  
Attn: TSCA Section 8(e) Coordinator  
Office of Pollution Prevention and Toxics  
U.S. Environmental Protection Agency  
Washington, D.C. 20460-0001

EPA looks forward to continued cooperation with your organization in its ongoing efforts to evaluate and manage potential risks posed by chemicals to health and the environment.

Sincerely,

Terry R. O'Bryan  
Terry R. O'Bryan  
Risk Analysis Branch

Enclosure

12759 A



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## Triage of 8(e) Submissions

Date sent to triage: DEC 14 1994

NON-CAP

CAP

Submission number: 12759A

TSCA Inventory:

Y    N    D

Study type (circle appropriate):

Group 1 - Dick Clements (1 copy total)

ECO                  AQUATO

Group 2 - Ernie Falke (1 copy total)

ATOX                  SBTOX                  SEN                  w/NEUR

Group 3 - Elizabeth Margosches (1 copy each)

STOX	CTOX	EPI	RTOX	GTOX
STOX/ONCO	CTOX/ONCO	IMMUNO	CYTO	NEUR

Other (FATE, EXPO, MET, etc.): \_\_\_\_\_

Notes:

**THIS IS THE ORIGINAL 8(e) SUBMISSION; PLEASE REFILE AFTER TRIAGE DATABASE ENTRY**

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entire document:  0     1     2    pages 1    pages 1, TAB

Notes: 2-sided

Contractor reviewer: Pat

Date: 11/1/94

## CECATS TRIAGE TRACKING DBASE ENTRY FORM

CFCATS DATA:

Submission # BEHQ-1293-12759

SEQ. A

TYPE INT SUPP FLWP

SUBMITTER NAME: Monsanto Company  
(Chemical Group)

SUB. DATE: 12/08/93 OTS DATE: 12/14/93 CSRAD DATE: 05/19/94

CHEMICAL NAME:

Flexzone 3C

## INFORMATION REQUESTED: FLY P DATE:

- 0501 NO INFO REQUESTED  
 0502 INFO REQUESTED (TECH)  
 0503 INFO REQUESTED (VOL ACTIONS)  
 0504 INFO REQUESTED (REPORTING RATIONALE)  
**DISPOSITION:**  
 0639 REFER TO CHEMICAL SCREENING  
 0678 CAP NOTICE

## VOLUNTARY ACTIONS

- 0401 NO ACTION REPORTED  
 0402 STUDIES PLANNED UNDERWAY  
 0403 NOTIFICATION OF WORKERS/STUDY  
 0404 LABEL/MSDS CHANGES  
 0405 PROCESS/HANDLING CHANGES  
 0406 APP/USE DISCONTINUED  
 0407 PRODUCTION DISCONTINUED  
 0408 CONFIDENTIAL

CASE#

101-72-4

## INFORMATION TYPE:

P.F.C.

- 0201 ONCO (HUMAN)  
 0202 ONCO (ANIMAL)  
 0203 CELL. TRANS (IN VITRO)  
 0204 MUTA (IN VITRO)  
 0205 MUTA (IN VIVO)  
 0206 REPRO/TERATO (HUMAN)  
 0207 REPRO/TERATO (ANIMAL)  
 0208 NEURO (HUMAN)  
 0209 NEURO (ANIMAL)  
 0210 ACUTE TOX. (HUMAN)  
 0211 CHR. TOX. (HUMAN)  
 0212 ACUTE TOX. (ANIMAL)  
 0213 SUB ACUTE TOX (ANIMAL)  
 0214 SUB CHRONIC TOX (ANIMAL)  
 0215 CHRONIC TOX (ANIMAL)

## INFORMATION TYPE:

P.F.C.

- 0216 EPICLIN  
 0217 HUMAN EXPOS (PROD CONTAM)  
 0218 HUMAN EXPOS (ACCIDENTAL)  
 0219 HUMAN EXPOS (MONITORING)  
 0220 ECO/AQUA TOX  
 0221 ENV. OCCC/REL/FATE  
 0222 EMER INCI OF ENV CONTAM  
 0223 RESPONSE REQUEST DELAY  
 0224 PROD/COMP/CHEM ID  
 0225 REPORTING RATIONALE  
 0226 CONFIDENTIAL  
 0227 ALLERG (HUMAN)  
 0228 ALLERG (ANIMAL)  
 0239 METAB/PHARMACO (ANIMAL)  
 0240 METAB/PHARMACO (HUMAN)

## INFORMATION TYPE:

P.F.C.

- 0241 IMMUNO (ANIMAL)  
 0242 IMMUNO (HUMAN)  
 0243 CHEM/PHYS PROP  
 0244 CLASTO (IN VITRO)  
 0245 CLASTO (ANIMAL)  
 0246 CLASTO (HUMAN)  
 0247 DNA DAM/REPAIR  
 0248 PROD/USE/PROC  
 0251 MSDS  
 0299 OTHER

- 01 02 04  
 01 02 04  
 01 02 04  
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 01 02 04

TRIAGE DATA

NON-CBI INVENTORY

YES

ONGOING REVIEW

YES (DROP/REFER)

SPECIES

FAT

TOXICOLOGICAL CONCERN:

USE:

PRODUCTION:

NO

10-12 months

NO (CONTINUE)

8-10 mo

LOW

MED

HIGH

Non-Cap garage, development

125 & 625 - increased food consumption, big increase incidence of gingival and/or facial delayed ossification  
 12.5 mg/kg - delayed ossification of facial bones  
 NO AEL not determined for fetotoxicity  
 for dam 12.5 mg/kg is NO AEL